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Archives of Internal Medicine

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# STUDIES ON THE RESPONSES OF THE CIRCULATION TO LOW OXYGEN TENSION

## III. CHANGES IN THE PACEMAKER AND IN CONDUCTION DURING EXTREME OXYGEN WANT AS SHOWN IN THE HUMAN ELECTROCARDIOGRAM *

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Anoxemia in the normal man can safely be carried to the stage of unconsciousness when produced by the process of continuous and gradual reduction of the oxygen in the air breathed. The responses of the body to the gradual oxygen reduction are compensatory to a certain limit. The crisis appears promptly when the compensating limit is reached for any particular person and set of experimental conditions until in rapid succession the following states are passed: (1) Decrease and loss of attention; (2) loss of voluntary control of muscles, and (3) complete unconsciousness but with a degree of reflex control of voluntary muscles. The heart beat and respiratory movements persist through these three cycles. The degree of circulatory efficiency at the onset of unconsciousness is adequate for the moment, but is assumed, in general, to be failing rapidly.

We have applied the methods of the electrocardiograph to the study of the changing function of the human heart through all stages of the symptoms of low oxygen from the normal to unconsciousness and collapse. Twenty-one cases are recorded in this paper.

The physiology of the human at high altitude has received consideration for the last half century, and the literature is now rather definite and in harmony as to the main causal explanations. The reader is referred to the phenomena described as mountain sickness by mountain climbers, or altitude sickness of balloon men, and to the corresponding symptoms detailed by those who have investigated the problem of low pressure chambers and of airplanes. The work of Paul Bert,[1] published in a series of scientific papers at intervals from 1871 to 1874 and in book form[2] in 1874 (summary) and 1878, of

* The experimental data detailed in this paper were obtained in a special study carried on under the orders of the Surgeon-General's Office, Division of Aeronautics.

1. Bert: A series of thirteen articles published from 1871 to 1874, Compt. rend. Acad. d. sc. **73**:213, 503, 1871; **74**:617, 1872; **75**:29, 88, 491, 543, 1872; **76**:443, 578, 1276, 1493, 1873; **77**:531, 1874; **78**:911, 1874.

2. Bert: La Pression Barometrique, etc., Paris, 1874 and 1878.

Mosso,[3] of Zuntz,[4] and the more exhaustive Pike's Peak studies of Douglas, Haldane, Henderson and Schneider,[5] have given the facts in the physiologic responses of the body in great detail. This accumulated altitude physiology became of immediate practical value with the development of the aviation program of the United States, and served as the scientific basis for the establishment of the Medical Research Laboratory of the Air Service.

Instances of unconsciousness developed in the air are related by men in the Air Service. Many aviation fatalities are thought to be due to this cause. Instances of unconsciousness or partial unconsciousness with physical distress developed at high altitudes have ended in recovery on descent to lower atmospheric levels. The experimental observations of the Medical Research Laboratory recorded in the Air Service Medical[6] support the view that these problems of altitude are not so much the effects of decrease in barometric pressure, or of temperature changes, but are primarily due to oxygen want.

The cardiac accelerations of rate due to progressive oxygen want were first described by Bert[7] in the experimental production of low atmospheric pressure in the low pressure chamber. Bert showed also that the accelerations were removed on giving oxygen in the chamber. The changes in rate are given in fuller detail with numerous illustrations, both for the low pressure chamber and the rebreather, by Schneider,[8] Whitney[9] and more fully in the Air Service Medical. Coincident changes in blood pressure, respiratory volume and alveolar air have been compared by Lutz and Schneider[10] and by Gregg, Lutz and Schneider.[11] The summarized facts and interpretative views may be stated catagorically for the heart as follows: The heart rate augments during oxygen reduction. Acceleration is slight and very gradual in the early stage of reduction, becomes more pronounced at from 15 to 12 per cent. oxygen, and very profound at the lowest limit of endurance by the individual, which may reach 7 or even 6 per cent., from 53 to 45 mm. partial pressure, in men of the highest oxygen resistance. Heart strain with dilation, circulatory collapse and fainting are described and emphasized by Whitney as a terminal condition to be avoided.

3. Mosso: Life of Man on the High Alps, London, 1898.
4. Zuntz, Loewy, Müller and Caspari: Hohenklima und Bergewanderung, etc., Berlin, 1906.
5. Douglas, Haldane, Henderson and Schneider: Phil. Tr. Roy. Soc., London, Series B, **203**:271, 1913.
6. Air Service Medical: U. S. War Department, Government Printing Office, 1919.
7. Bert: Compt. rend. Acad. d. sc. **78**:911, 1874.
8. Schneider: J. A. M. A. **71**:1384 (Oct. 26) 1918.
9. Whitney: J. A. M. A. **71**:1389 (Oct. 26) 1918.
10. Lutz and Schneider: Am. J. Physiol. **50**:228, 280, 327, 1919.
11. Gregg, Lutz and Schneider: Am. J. Physiol. **50**:302, 1920.

Of the points summarized, the variations in heart rate may be accepted without question. The seven thousand and more records of official tests of aviators substantiate these facts. On the other hand, the cardiac dilation assumed on the basis of percussion has been more and more strongly questioned as the tests have accumulated. The determination of relative cardiac volume, minute by minute, is, in fact, fraught with great difficulty. The usual palpation and percussion methods are scarcely accurate enough to decide the point. The roentgen-ray method yields results that must be correlated with the phases of both the cardiac cycle and the respiratory movement, which for the moment vary the size of the heart. Majors Le Wald and Turrell [12] have applied ingenious devices to secure photographs at corresponding phases of the heart and respiratory cycles in their roentgen-ray studies of the size of the heart during progressive low oxygen induced by the rebreather method. They find little evidence of change of heart volume. This finding accords with the measurements of the circulation volume by Schneider and Sisco on Pike's Peak,[13] data from which the conclusion was drawn that the heart volume does not change with the increase of rate up to the altitude of Pike's Peak, i.e., 14,110 feet. However, 14,000 feet does not reach the straining limits of compensation for the average vigorous man. From 20,000 to 30,000 feet, and more, must be reached to produce the extreme vascular changes. Le Wald and Turrell describe one case of unconsciousness at the moment of a roentgen-ray exposure. This heart was not dilated. On the contrary, its outlines and volume were notably less than those shown by pictures taken at earlier stages of oxygen want from the same officer.

## THE ELECTROCARDIOGRAPHIC METHODS

Electrocardiograms offer an added approach to the state of the heart under oxygen want. The method cannot lay claim to even a probable solution to the heart volume problem. But it ought to yield facts of value to the interpretation of the physiological state of the heart under extreme low oxygen stress and the possible source of the collapse in the circulatory system.

The electrocardiographic method is the present reliance for the determination of the following points in heart physiology:

1. The place of origin of the automatic excitation process.
2. The state, rate and direction of conduction of the excitation over the heart.
3. The degree of coordination of different parts of the heart.
4. The character of extra systoles of diverse types.

12. LeWald and Turrell: Am. J. Roentgenol. **7**:67, 1920.
13. Schneider and Sisco: Am. J. Physiol. **34**:1, 1914.

The oxygen want test was given to twenty-one individuals from whom electrocardiograms were taken at stated intervals during the tests. The experiments were made at the U. S. General Hospital No. 9, at Lakewood, N. J., March 5 to 12, 1919. All the necessary rebreather apparatus and the staff of assistants were taken to the Lakewood Hospital from Hazelhurst Field, Long Island. This secured to us the facilities of the excellent electrocardiographic station at Hospital No. 9.

The procedure was, in brief, to give the official rebreather test on the Larsen-Pierce type of rebreather. During the test the systolic and diastolic blood pressures, the heart rates, the respiratory movements, the respiratory minute-volumes, and the clinical state of the individual were all taken as described in the statement of methods in the various papers from the Medical Research Laboratory.

Electrocardiograms were taken for periods of about twenty seconds each, at five minute intervals, until the critical period or final failure of compensation approached. In most tests the interval was reduced to two minutes after the twentieth minute. At the critical moment and on signal from the clinician, a continuous electrocardiogram was taken until the end of the test. A final tracing was then taken after one or two minutes, and while recovery was in progress. Occasionally, due to the rapid onset of symptoms of oxygen want, the terminal tracing was missed, or the last asphyxial tracing was extended across to the recovery period. Through the hearty cooperation of the enlisted personnel of the Lakewood Hospital, splendid rebreather tests were carried to the limits of consciousness, and in several instances even beyond the point of complete loss of motor control by the central nervous system.

Loss of continuous attention and of voluntary motor coordination are the usual signs for terminating an official rebreather test. But heart and circulatory compensations continue several seconds longer, i. e., certainly until complete unconsciousness occurs. This is the rule. In exceptional cases, circulatory failures of compensation rather than failure of nervous coordinations occur at relatively high percentages of oxygen.

The official psychologic and ocular tests in use at the central laboratory at this time were abandoned as unnecessarily complicating this research. In judging the safe terminal limits of endurance, reliance was placed on the recorded evidences of compensations of respiratory volume, the coincident heart rate and blood pressure, and the general clinical signs of distress. The men who take this test, even to the limit of unconsciousness, recover very promptly after one or two inhalations of ordinary air. The delay is only a question of a few seconds, and the subject tested cannot believe that he has not been continuously

conscious. Friendly and keen rivalry among the men at Lakewood often led to protest that they had not yet reached their altitude limits, which indicates the absence of physical stress.

## GENERAL EXPERIMENTAL RESULTS

Our results are presented in two groups. First, and briefly, the general observations necessary to the interpretation of the electrocardiographic results; second, the details of the changes in the heart recorded by the electrocardiograph. The general changes have to be kept clearly in the foreground that one may correctly interpret the changes in the heart itself.

By our method we not only record the electrocardiograms but also the respiratory rate, amplitude and volume. We take clinical observations of the heart rate and measure the blood pressures every minute by the sphygmomanometer method. The clinical aspect of the changes we present by a series of protocols and graphic charts (Figs. 1 to 7). Numerous published typical charts of this test are available in the Air Service Medical.[6] Only the cases of special interest in our series are charted here.

The chart presented for H. B. D. (Fig 1) serves very well to emphasize the critical points in the interpretation of the clinical results. His heart rate gradually increased from a minimum of 82 per minute to a maximum of 114 in the twenty-sixth minute when the break occurred. The systolic blood pressure increased during the run from 128 mm. to 152 mm. at the break. The diastolic pressure ran evenly enough at 70 mm. to the nineteenth minute, then progressively and rapidly fell to 50 at the break, 34 at the last reading. Up to the point of breaking, this record is a fairly typical one in regard to the compensatory responses of the circulatory system. Although the systolic pressure was always somewhat high for an average individual, the respiratory minute volume remained very low and irregular to the twenty-third minute, when it rapidly increased from 70 to 104 deciliters per minute. This was a strong test to 6.7 per cent. oxygen, over 29,000 feet equivalent elevation and over 27,000 feet when systolic pressure began to fall. The weakest clinical factor is apparently in the respiratory apparatus which did not compensate enough to prevent collapse, unconsciousness, clonic spasms and circulatory failure.

Comparing the seven charts it is obvious that F. J. D. (Fig. 2) also failed because of the respiratory deficit. J. F. (Fig. 3) collapsed at 8.4 per cent. oxygen from general failure of compensation in both blood vascular and respiratory mechanisms. His systolic pressure decreased from the beginning. There was some cardiac acceleration but absolutely no respiratory response. The limit of the endurance of T. H. K. (Fig. 4) was over 28,000 feet, 7.1 per cent. oxygen. In his case

there was inadequate circulatory compensation. The lowest oxygen endured in this series was W. C. M. (Fig. 5) at 5.9 per cent. altitude, over 31,000 feet. This was accomplished largely by virtue of an extraordinary response of the respiratory apparatus and a rising blood pressure. Even at that altitude (Plate 4) only the slightest shift in the locus of the point of origin of the heart beat occurred. The collapse of T. B. M., like that of J. F., was a failure of compensation in blood pressure. Both systolic and diastolic pressure fell from the start. The increase in heart rate and change in respiratory volume is not adequate as the final break showed. The profound heart failure in D. W. O. (Fig. 7) came at the comparatively high oxygen level of 8.5 per cent. This case is a fine example of a noncompensating type which endures oxygen want to its particular limit, then suddenly and without warning collapses.

The cases are fully illustrated because they fall in the class that gave cardiac breaks, and are all good tests for rather extreme low oxygen endurance. In fact, 8.5 per cent. oxygen is the highest of the lot. And while the cause of failure is more or less easy to interpret, it is also true that the tests were deliberately pressed to the extreme to secure data on the postcrisis and collapse stage. The cases are, therefore, not to be regarded as being pathologic.

The tests on seven out of twenty-one men examined gave valuable postcrisis data in cardiac behavior, and this data will be presented in full detail in the protocols.

### ELECTROCARDIOGRAPHIC RESULTS

The electrocardiographic data are presented in detail in tables of measurements of cardiograms taken at intervals during the tests and the tables are supported by photographs of selected pieces of electrocardiograms. The protocols, tables, and plates give the first published data on the terminal stress of progressive oxygen want on the human heart, an adequate justification for full presentation of the data. Nevertheless, we have many additional cases and much evidence in reserve supporting the cases presented.

Profound changes are revealed in the physiology of the heart in the seven extreme tests featured. But take it all in all, the entire series shows a wonderful amount of endurance to oxygen want on the part of the human heart. Rarely does any serious interference with the normal cardiac behavior occur up to the stage which marks the borderland between loss of individual efficiency and complete unconsciousness.

The R-R interval is, of course, a function of the heart rate. The rate augments during the precrisis stage of the low oxygen test, at first slowly and then more rapidly. This is the observation of fact

previously well established as a typical compensatory response of the heart during the official altitude test.

The so-called sinus arrhythmia, present in most individuals, is accentuated during the early period of the altitude test in many. This fact makes it difficult to select at random individual pulses in any two periods under comparison that represent exactly the same phase in the sinus variations. On the whole, the cycles measured vary in fair agreement with the clinical increases in rate noted in the radial counts by twenty second intervals.

The oxygen left in the rebreather was determined at the close of each test. In the graphs the terminal oxygen percentage is recorded over the minute at which the test was closed. On the assumption that oxygen consumption was constant minute by minute, a straight line is drawn from the point on the chart at the beginning of the test at 21 per cent. oxygen to the point in the scale representing the terminal percentage at the time of the close of the test. This is the practice in recording the Air Service tests. The percentage of oxygen at any minute in the test can be read off directly from the chart. This method of reading is the one used in determining the oxygen of the air breathed at the various intervals at which cardiograms are shown in the plates.

## PROTOCOLS OF OBSERVATIONS CONNOTING TERMINAL HEART FAILURE OF VARIOUS TYPES

PROTOCOL 1.—Sgt. H. B. D.; oxygen reached 6.7 per cent.; time, 27 minutes, 20 seconds.

The physiologic and clinical responses recorded minute by minute through the entire test are presented in Figure 1. The chart shows very good compensations through to the end of the twenty-sixth minute. During the twenty-seventh minute, the systolic blood pressure fell sharply from 152 to 126 mm., and to 111 mm. at the first blood pressure reading after the experiment. In the interim, the systolic pressure had been lower, as indicated by the further rise of pressure to 134 mm. on the third reading of the recovery.

The heart gave a fine compensatory increase of rate to the twenty-seventh minute. The clinical chart indicates a gradual and normal return to the pre-experiment level. However, the electrocardiogram taken after the twenty-seventh minute and just before the close of the test, shows a rate of only 70. This rate dropped to 68 at the beginning of the recovery electrocardiogram (Fig. 1, E-R). This electrocardiographic rate occurred between the last clinical test and the first recovery rate recorded. The true curve, therefore, shows a sharp fall, to the marks E-R, and then a rise of 22 mm. to the clinical recovery rate. It is assumed that the fall in systolic blood pressure and in heart rate are, in fact, simultaneous although recorded in sequence.

The respiratory minute volume varied greatly, between 54 and 81 deciliters per minute to the twenty-third minute, an average between 65 and 70. During the last three minutes, the volume ran up to 103 deciliters, which in itself is good but not full compensation for the reduction of oxygen below 7 per cent.

During the first seven records, including the twenty-fourth minute, the electrocardiograms show the typical variations. There was a decided sinus arrhythmia. The extreme rates during the arrhythmia are indicated by the

pairs of measurements in the tenth, fifteenth, twentieth, twenty-second and twenty-fourth minutes. In the twentieth minute, oxygen 10.5 per cent., the sinus arrhythmia varied from 0.548 to 0.784 second per single beat, i. e., theoretical rates of 110 and 76 beats per minute. These variations occur within the time between the sixth and sixteenth beats.

During the extreme changes in rate there is little change in the P-R interval, a maximum variation of 0.008 second in this case. On the other hand, the R-T shortens with the acceleration of rate, i. e., as the oxygen decreases. Apparently, it is the oxygen factor that is involved, since in the shorter beat

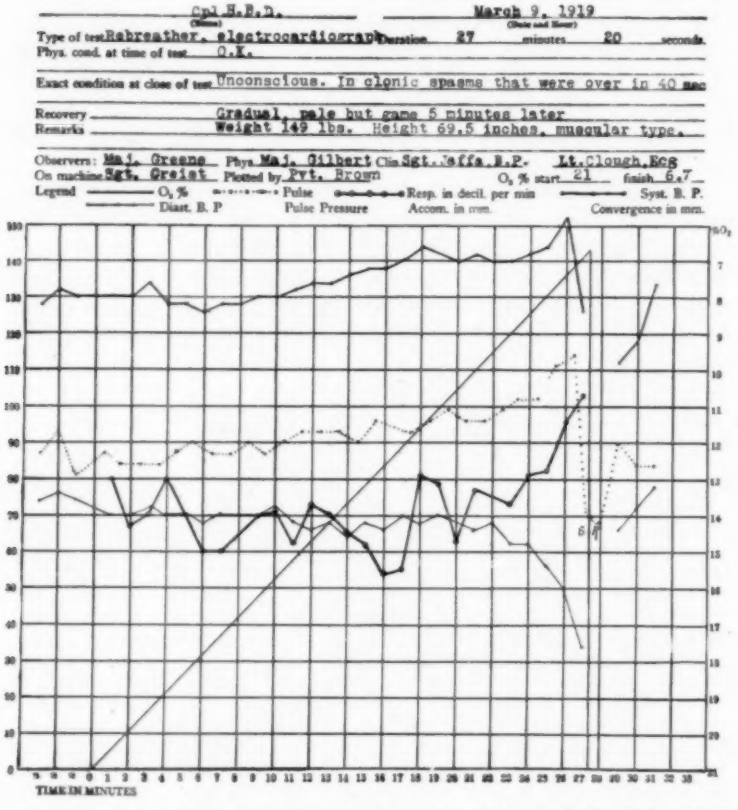
Cpl H.E.D.
March 9, 1919
Type of test Rebreather, electrocardiograph Duration 27 minutes 20 seconds
Phys. cond. at time of test O.K.
Exact condition at close of test Unconscious. In clonic spasms that were over in 40 sec
Recovery Gradual, pale but game 5 minutes later
Remarks Weight 149 lbs. Height 69.5 inches, muscular type.
Observers: Maj. Greene Phys. Maj. Gilbert Clin. Sgt. Jaffa, R.P. Lt. Clough, Eng
On machine Sgt. Greist Plotted by Pvt. Brown O2 % start 21 finish 6.7
Legend O2 % Pulse Resp. in decil. per min Syst. B. P.
Diast. B. P Pulse Pressure Accom. in mm. Convergence in mm.
TIME IN MINUTES

Fig. 1.—The clinical charts show the percentage of oxygen in the air breathed, oblique line; the heart rate, dotted line; systolic blood pressure, the top line; the diastolic blood pressure, the bottom line; and the volume per minute of air breathed, heavy line. E. R., the rate computed from the electrocardiographic record at the moment the test was closed and 20 seconds later. The long spaced stipples indicate the heart rate shifts between the pre- and post-clinical rates as determined by the electrocardiogram. The blood pressures in mm. mercury, heart rates per minute, and deciliters of air per minute are indicated in the legend to the left; the percentage of oxygen to the right. This legend answers for Figures 1 to 7, inclusive.

given for the normal, 0.628 second, the R-T interval is 0.320 second, whereas in the twentieth minute the pulse of 0.784 second duration shows an R-T interval of 0.300 second.

In the energy of the deflections, the P wave is comparatively constant. The negative Q, which is present in this case, is relatively constant though it decreases with the onset of low oxygen. The R also decreases in amplitude. The S varies through a wide range. The T is diminished by at least half and is somewhat lower in the pulses of shortest duration.

When the test reached 6.8 per cent. oxygen in the twenty-seventh minute, decided changes occurred in the character of the electrocardiogram which are of greatest importance in tracing the onset of cardiac collapse. They did not

TABLE 1.—Sgt. H. B. D., March 9, 1919

Time of run 27 minutes 20 seconds. Final oxygen, 6.7 per cent.

| Trace and Pulse No. | Time | Oxygen, per Cent. | Duration in Sec. | | | Amplitude in Mm. | | | | | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | R-R | P-R | R-T | P | Q | R | S | T | |
| 1-5 | Normal | 21.0 | 0.628 | 0.140 | 0.320 | 1.5 | 2.0 | 16.0 | 4.0 | 3.5 | Sinus arrhythmia |
| 1-21 | Normal | 21.0 | 0.628 | 0.140 | 0.320 | 2.0 | 2.0 | 16.0 | 2.0 | 4.0 | shown by variation of R-R |
| 2-1 | 5 min. | 18.4 | 0.540 | 0.140 | 0.320 | 1.8 | 2.0 | 14.0 | 2.5 | 2.5 | Arrhythmia slow and marked |
| 3-1 | 10 min. | 15.7 | 0.800 | 0.140 | 0.320 | 1.4 | 1.2 | 15.0 | 3.0 | 2.8 | |
| 3-7 | 10 min. | 15.7 | 0.612 | 0.144 | 0.320 | 1.6 | 1.4 | 13.0 | 2.0 | 2.4 | |
| 4-5 | 15 min. | 13.1 | 0.776 | 0.144 | 0.300 | 4.6 | 1.0 | 15.5 | 4.0 | 2.0 | |
| 4-1 | 15 min. | 13.1 | 0.560 | 0.136 | 0.312 | 2.0 | 2.0 | 14.0 | 3.0 | 2.2 | |
| 5-6 | 20 min. | 10.5 | 0.784 | 0.144 | 0.300 | 1.6 | 1.3 | 16.5 | 4.5 | 2.0 | Long period arrhythmia |
| 5-16 | 20 min. | 10.5 | 0.548 | 0.136 | 0.292 | 1.6 | 1.0 | 13.0 | 2.0 | 1.8 | |
| 6-6 | 22 min. | 9.5 | 0.760 | 0.136 | 0.300 | 1.5 | 1.0 | 16.0 | 4.0 | 2.0 | |
| 6-16 | 22 min. | 9.5 | 0.520 | 0.144 | 0.292 | 2.0 | 1.4 | 12.5 | 2.0 | 1.8 | |
| 7-1 | 24 min. | 8.4 | 0.648 | 0.144 | 0.300 | 1.8 | 1.3 | 14.5 | 3.0 | 2.0 | Sinus arrhythmia |
| 7-7 | 24 min. | 8.4 | 0.504 | 0.136 | 0.304 | 1.8 | 1.2 | 13.0 | 2.5 | 2.0 | |
| 8-1 | 26 min. | 7.4 | 0.540 | 0.140 | 0.296 | 1.0 | 1.6 | 13.0 | 4.0 | 2.2 | |
| 9-1 | 27 min. | 6.8 | 0.760 | none | 0.300 | none | 2.0 | 16.0 | 1.0 | 3.0 | Colonic spasms at end of Experiment P not evident |
| 10-2 | Recovery | 21.0 | 0.868 | none | 0.320 | none | 2.0 | 18.0 | 2.0 | 3.4 | |
| 10-3 | Recovery | 21.0 | 0.832 | none | 0.320 | none | 1.6 | 15.0 | 2.0 | 3.2 | |
| 10-4 | Recovery | 21.0 | 0.812 | none | 0.320 | none | 1.6 | 16.0 | 2.0 | 3.0 | |
| 10-5 | Recovery | 21.0 | 0.760 | 0.064 | 0.320 | 1.2 | 0.0 | 17.0 | 2.0 | 3.2 | |
| 10-6 | Recovery | 21.0 | 0.760 | 0.128 | 0.320 | 2.0 | 1.2 | 14.5 | 2.5 | 3.6 | |
| 10-7 | Recovery | 21.0 | 0.700 | 0.144 | 0.328 | 2.0 | 1.0 | 14.0 | 2.5 | 4.0 | |
| 10-8 | Recovery | 21.0 | 0.560 | 0.140 | 0.320 | 2.0 | 1.0 | 14.0 | 3.4 | 4.2 | |
| 10-9 | Recovery | 21.0 | 0.640 | 0.144 | 0.320 | 1.8 | 0.6 | 14.0 | 3.0 | 4.0 | |
| 10-10 | Recovery | 21.0 | 0.868 | 0.140 | 0.320 | 2.0 | 0.6 | 13.5 | 3.0 | 4.0 | |
| 10-19 | Recovery | 21.0 | 0.872 | 0.128 | 0.320 | 1.6 | 1.0 | 15.0 | 3.0 | 4.5 | |

come on until the approach of unconsciousness which was coupled in this man with intense clonic muscular spasms at the close of the test. These clonic spasms are in themselves of special significance since the man was a vigorous neuromuscular type and in the best of physical condition.

A short cardiogram was obtained just before the experiment ended. The heart rate had slowed down to between 75 and 80 per minute from a previous rate of 111 in the twenty-sixth minute. The ventricular complexes are of the normal type. Although the presence of extraneous currents from the clonus destroyed the regularity of the record no P wave could be detected. It is apparent that in the unrecorded interval, the P wave had dropped out. In other words, the sino-auricular pacemaker no longer gave evidence of functioning. The normal type of ventricular complex shows that the auriculoventricular pacemaker controlled this rhythm. This is a case of suppression of the sino-auricular beat, similar to Lewis' experiment on the cat heart. An alter-

native hypothesis would assume that the P wave is buried in some part of the R-S-T complex, but the ventricular complex is like the normal in amplitude and duration. A careful comparison with the earlier normals gives no suggestion of a superimposed P wave occurring in any portion of the ventricular complex, although this does not preclude the possibility of such an inclusion. If we assume that the P is completely suppressed, then we would have at the same time to accept the deduction that reversed conduction from the A-V node is also suppressed. This point cannot be proven from this particular test, but a suppression of conduction does seem to occur in the test of Cpl. F. J. D. in whom there is dissociation of auricular and ventricular rhythms (Table 2).

In the after period the first three ventricular complexes are not associated with P waves. In the fourth contraction, there is a P wave with a P-R interval of 0.060 second. Table 1 presents the series of measurements for the first ten contractions and the nineteenth or last of the series. In the first, second and third, there is no evidence of an auricular contraction. In the fourth beat, the P wave appears 0.064 second in advance of the R wave. In the fifth it is 0.128 second, and in the succeeding sixth to the eighteenth beats the intervals are again normal, 0.140 second. During this series the ventricular complex is normal in type. It is constant in duration, namely 0.320 second. A rather striking point is the acceleration of the rate with the reappearance of sino-auricular control of the contraction. The rate accelerates through the equivalents of 68, 69, 72, 74, 81, 81, 86, 95, 94; then slows to 68, 71, 68, 68, 68, 70, 70, 69, 69, during the reestablishment of the normal relations. Progressive and gradual recovery of the pace-making function in the ascending direction is indicated. During the suppression of the P wave, the origin of the beat is in the A-V nodal tissue. In the fourth and fifth beats, it is higher up, and on and after the sixth beat it apparently occurs in the S-A node, as indicated by the normal conduction time. The slower rate introduced at the tenth beat is indicative of returning vagal tonic control of the rhythm.

TABLE 2.—F. J. D., APRIL 9, 1919

Time of run 24 minutes, 26 seconds. Final oxygen, 8.1 per cent.

| Trace and Pulse No. | Time | Oxygen, per Cent. | Duration in Seconds | | | | Amplitude in Mm. | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | P-P | R-R | P-R | R-T | P | Q | R | S | T |
| 1-1 | Normal | 21.0 | 0.920 | 0.920 | 0.344 | 0.344 | 1.3 | none | 10.0 | 2.5 | +0.6 to —0.2* |
| 2-2 | 5 min. | 18.4 | 0.828 | 0.824 | 0.308 | 0.360 | 1.5 | none | 9.6 | 2.0 | +0.7 to —0.6 |
| 3-2 | 10 min. | 15.8 | 0.800 | 0.804 | 0.320 | 0.360 | 1.4 | 0.3 | 9.4 | 2.0 | +0.6 to —0.7 |
| 4-6 | 15 min. | 13.1 | 0.748 | 0.744 | 0.316 | 0.344 | 1.6 | 0.3 | 9.0 | 2.0 | +0.6 to —0.4 |
| 5-1 | 20 min. | 10.5 | 0.800 | 0.792 | 0.296 | 0.328 | 1.2 | 0.8 | 9.2 | 3.0 | +0.2 to —0.8 |
| 6-2 | 22 min. | 9.4 | 0.728 | 0.716 | 0.296 | 0.336 | 1.8 | 0.4 | 9.0 | 3.2 | +0.6 to —0.8† |
| 7-1 | 24 min. | 8.1 | 0.680 | 0.680 | 0.308 | 0.336 | 1.0 | trace | 9.0 | 3.0 | +0.7 to —0.2 |
| 8 | "off" Last pulse | 21.0 | 0.712 | 0.712 | 0.314 | 0.342 | 2.0 | none | 9.0 | 3.0 | —0.2 to —tr. |
| 7-1 | Five successive pulses in the 24th minute | 8.1 | 0.680 | 0.680 | 0.308 | 0.336 | 1.0 | trace | 9.0 | 3.0 | +0.7 to —0.2 |
| 7-2 | | 8.1 | 0.728 | 0.680 | 0.288 | 0.344 | 1.5 | 0.4 | 9.0 | 3.0 | +0.8 |
| 7-3 | | 8.1 | 0.784 | 0.692 | 0.212 | 0.320 | 1.5 | trace | 8.0 | 2.4 | +0.6 |
| 7-4 | | 8.1 | 0.896 | 0.716 | 0.112 | 0.320 | 1.6 | trace | 8.0 | 3.0 | +0.4 |
| 7-5 | | 8.1 | 0.900 | 0.740 | 0.048‡ | 0.340 | 1.6 | none | 8.0 | 3.0 | +1.2 |

* T = di-phasic, in some pulses, +0.6 to —0.4 and more.
† Complete block developed. See Table 5. T = di-phasic.
‡ R-P interval.

PROTOCOL 2.—Cpl. F. J. D.; oxygen 8.1 per cent.; time 24 minutes, 26 seconds.

The clinical sheet of Cpl. F. J. D. shows compensations of the circulatory system to 10 per cent. oxygen (Fig. 2). The normal heart rate of 63 was augmented to 96 during the twenty-second minute, then fell sharply during the twenty-third and twenty-fourth minutes. The systolic blood pressure was sustained to the end of the experiment, but diastolic pressure broke at twenty-

one minutes. The electrocardiogram in the twenty-fourth minute shows the onset of complete heart block. This is coupled with a slow ventricular rate. It is interesting that the systolic pressure was maintained for a few moments in the presence of both slow heart rate and sharp diastolic break. There was complete failure of compensation in respiration. The very large minute volume of air breathed in the sixth and seventh minutes was due to a series of deep sighing inspirations. In fact, the whole respiratory record was extremely irregular in tidal volume.

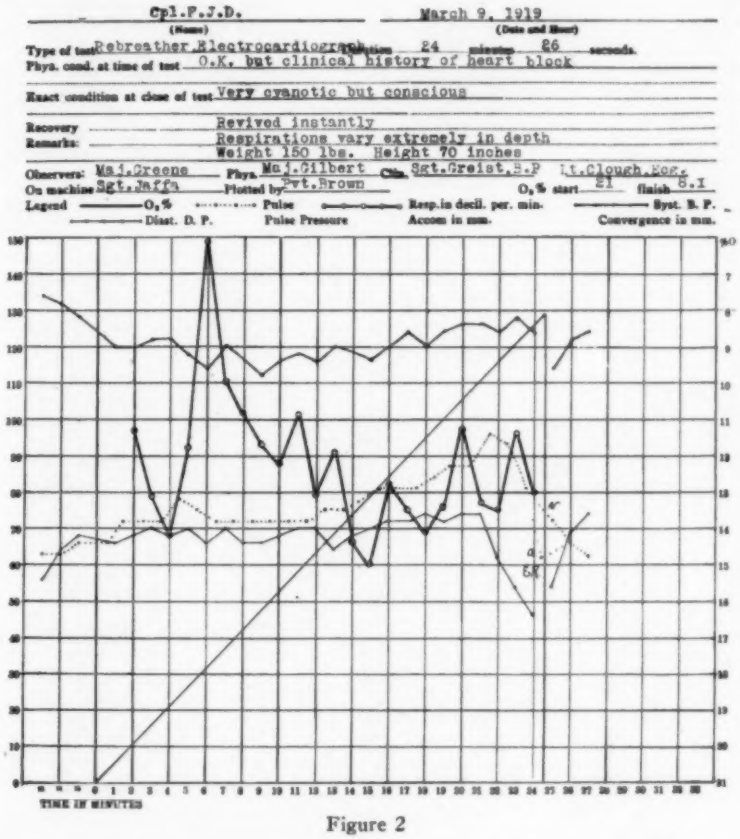
Cpl.F.J.D.
(Name)
March 9, 1919
(Date and Hour)
Type of test Rebreather Electrocardiograph
Duration 24 minutes 26 seconds.
Phys. cond. at time of test O.K. but clinical history of heart block
Exact condition at close of test Very cyanotic but conscious
Recovery Revived instantly
Remarks: Respirations very extremely in depth
Weight 150 lbs. Height 70 inches
Observers: Maj.Greene Phys. Maj.Gilbert Obs. Sgt.Greist,S.P Lt.Clough,Eng.
On machine Sgt.Jaffa Plotted by Pvt.Brown
O2% start 21 finish 8.1
Legend O2% Pulse Resp.in decil. per. min. Syst. B. P.
Diast. D. P. Pulse Pressure Accom in mm. Convergence in mm.
TIME IN MINUTES

Figure 2

Eight electrocardiograms were secured. Only slight changes in the form of the cardiogram occurred during the first twenty-two minutes. There was a shortening of the P-R time associated with the increase in heart rate. The normal time of contraction was 0.920 second, in the twenty-second minute, the last contraction of Figure 6, Plate I, the time of the beat was 0.716 second. Little change occurred in the time of the ventricular complex. The conduction time was exceptionally long, 0.344 second in the normal tracing, which is two and one-half times the normal average.

No striking changes occurred in the amplitudes of the different deflections. However, the entire series of records show diphasic T. waves. In some portions a distinct U wave also occurred (Plate I, Fig. 1, also in Fig. 3). The long conduction time is suggestive of some possible lesion in the conducting tissue, with corresponding delay in the process.

In the twenty-fourth minute a change occurred in the rhythm which admits of some discussion. The entire record secured at 8.1 per cent. is presented in Figures 7 and 8, Plate I. Inspection of this record shows that complete dissociation occurred. The first P-R interval of the record is slightly less than the normal for the individual, and each succeeding interval is decreased in time. At the same time, there is lengthening of the P-P interval, evidencing auricular slowing, while the R-R interval remains substantially the same, or does not increase in proportion. Two possibilities are suggested: first, that in the preceding unrecorded interval, conductivity had depressed, and that the dissociation is due to a final complete internodal block. Second, that the dissociation is due to the depression of the pace-making function of the sino-auricular node to a point below the rate of stimulus production inherent in the A-V node at that time, allowing the A-V node to assume the dominant rhythm. Independent rhythm cannot be induced by this second process, except when reverse block is present.

TABLE 3.—Cpl. F. J. D. Twenty-Fourth Minute. Oxygen 8.1 Per Cent.

Giving the auricular intervals, P-P, and the ventricular, R-R, and the time from the beginning of the auricular complex to the next succeeding ventricular complex. The series includes all the beats during the twenty-fourth minute, i. e., from the beginning of complete block to the end of the test. The block appeared at 8.1 per cent. oxygen.

| Ventricular Contraction Serial No. | Intervals in Seconds | | | Computed Rates | |
|---|---|---|---|---|---|
| | P-P | R-R | P-R | Auricular | Ventricular |
| 1 | 0.680 | 0.680 | 0.28 | 88 | 88 |
| 2 | 0.728 | 0.680 | 0.26 | 82 | 88 |
| 3 | 0.784 | 0.692 | 0.20 | 76 | 87 |
| 4 | 0.896 | 0.716 | 0.10 | 67 | 84 |
| 5 | ..... | 0.740 | .... | .. | 81 |
| 6 | 0.900 | 0.644 | 0.64 | 62 | 93 |
| 7 | 0.936 | 0.768 | 0.36 | 64 | 78 |
| 8 | 0.984 | 0.800 | 0.21 | 61 | 75 |
| 9 | 0.920 | 0.808 | 0.00 | 65 | 75 |
| 10 | ..... | 0.804 | .... | .. | 75 |
| 11 | 0.880 | 0.808 | 0.74 | 68 | 67 |
| 12 | 0.880 | 0.808 | 0.68 | 68 | 75 |
| 13 | 0.880 | 0.620 | 0.60 | 68 | 97 |
| 14 | 0.824 | 0.748 | 0.34 | 73 | 80 |
| 15 | 0.856 | 0.748 | 0.24 | 73 | 82 |
| 16 | 0.920 | 0.732 | 0.12 | 65 | 82 |
| 17 | ..... | 0.732 | .... | .. | 82 |
| 18 | 0.840 | 0.732 | 0.68 | 71 | 82 |
| 19 | 0.860 | 0.616 | 0.52 | 70 | 97 |
| 20 | 0.760 | 0.696 | 0.32 | 79 | 86 |
| 21 | 0.740 | 0.700 | 0.22 | 81 | 86 |
| 22 | 0.800 | 0.692 | 0.20 | 75 | 86 |
| 23 | 0.940 | 0.704 | 0.05 | 64 | 85 |
| 24 | ..... | 0.720 | .... | .. | 83 |
| 25 | 0.920 | 0.664 | 0.56 | 65 | 90 |
| 26 | 0.960 | 0.716 | 0.30 | 63 | 84 |

Whatever its etiology, dissociation clearly occurs. In this record the P wave is seen to move through the ventricular complex four times which argues against A-V control of the auricular rhythm. Table 3 shows a record of the measurements for the entire tracing. The recovery tracing (Plate I, Fig. 9) shows that the normal relationship has returned as regards the sequence. We feel that a depression of the rhythmicity of the sino-auricular node is definitely shown. In itself the record is insufficient wholly to justify this conclusion. But when compared with suppression of rhythm in the auricles of other hearts

to be described later, and with the added evidence that in routine Air Service examinations a decrease in rate was frequently observed in acute oxygen want, we feel that our conclusion is warranted.

PROTOCOL 3.—Pvt. J. F.; final oxygen, 8.4 per cent.; total time, 21 minutes, 56 seconds.

The clinical chart is of peculiar interest as a type showing sudden collapse at a comparatively high percent. of oxygen, between 9 and 10 per cent. There is a clinical history diagnosed as effort syndrome. The blood pressures, both systolic and diastolic, steadily fell to 9.5 per cent. oxygen when collapse began.

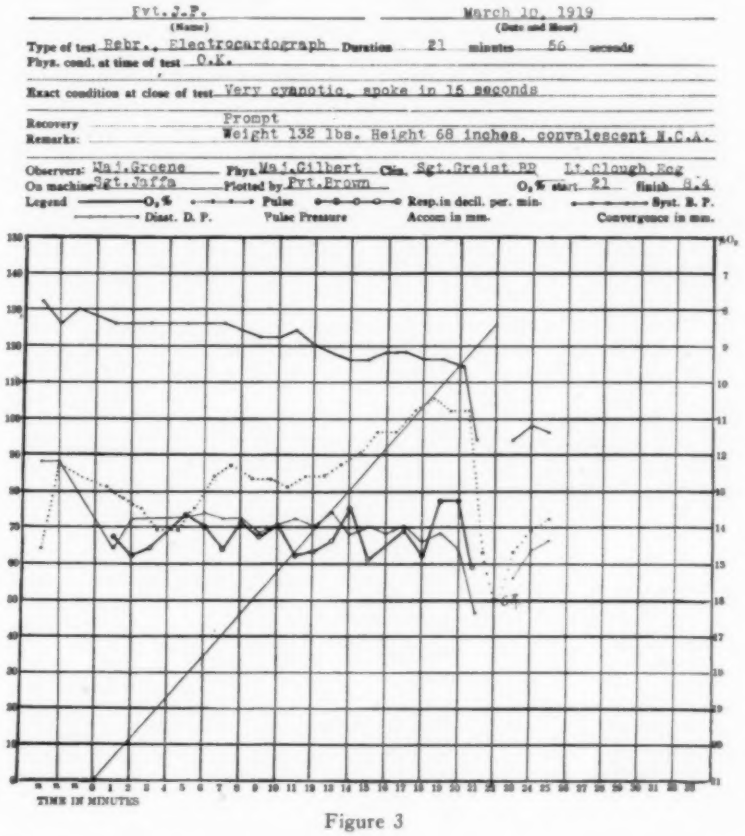
Pvt. J. F.
(Name)
March 10, 1919
(Date and Hour)
Type of test Rebr., Electrocardiograph Duration 21 minutes 56 seconds
Phys. cond. at time of test O.K.
Exact condition at close of test Very cyanotic, spoke in 15 seconds
Recovery Prompt
Remarks: Weight 132 lbs. Height 68 inches. convalescent U.S.A.
Observers: Maj. Greene Phys. Maj. Gilbert Clin. Sgt. Greist RD Lt. Clough, Eng
On machine Sgt. Jaffa Plotted by Pvt. Brown O2 % start 21 finish 8.4
Legend O2 % Pulse Resp. in decil. per min. Syst. B. P.
Diast. D. P. Pulse Pressure Accom in mm. Convergence in mm.
TIME IN MINUTES

Figure 3

There was no respiratory compensation during the entire run. The heart rate increased from a normal of 69 to a maximal of 105 in the nineteenth minute. In the last minute the rate fell from 102 to 63 at the last clinical count. The electrocardiogram of the twenty-first minute gives a rate of 68 (Plate 2, Fig. 6). In the electrocardiogram in the early recovery stage and just before the first clinical recovery record, the heart had slowed to an equivalent rate of 50 in the 4th beat (*E. R.*, Plate 2, Figs. 3 and 7). The clinical record shows the lack of compensatory elasticity in the effort syndrome type. The test was not

carried to the complete limit of endurance. The usual changes in the electrocardiogram with reduced oxygen appear only in the T wave. The P-R and R-T intervals are constant.

The chief interest in this test lies in the sudden reduction of heart rate in the twenty-first minute. The slow rate continued throughout the recovery record with pure air. The electrocardiogram is normal in form although the heart rate was reduced to 68 per minute just before the experiment ended, and to 50 per minute during the early recovery. The sudden slowing of the rate just at the close of the experiment is a typical instance of the effect of oxygen want in slowing stimulus production at the crisis.

TABLE 4.—Pvt. J. F., March 10, 1919

Time of run 21 minutes, 56 seconds. Final oxygen, 8.4 per cent.

| Trace and Pulse No. | Time | Oxygen, per Cent. | Duration in Sec. | | | Amplitude in Mm. | | | | | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | R-R | P-R | R-T | P | Q | R | S | T | |
| 1-2 | Normal | 21.0 | 0.668 | 0.140 | 0.306 | 1.4 | none | 9.0 | 0.7 | 4.0 | Effort syndrome case |
| 2-2 | 5 min. | 18.1 | 0.760 | 0.144 | 0.308 | 1.0 | none | 9.5 | 1.0 | 2.8 | |
| 3-4 | 10 min. | 15.3 | 0.700 | 0.148 | 0.304 | 1.0 | none | 9.0 | 1.0 | 3.0 | |
| 4-2 | 15 min. | 12.4 | 0.616 | 0.144 | 0.296 | 1.4 | none | 9.0 | 0.6 | 2.4 | Slight sinus arrhythmia |
| 5-2 | 20 min. | 9.5 | 0.560 | 0.140 | 0.292 | 1.4 | none | 10.5 | 0.4 | 1.6 | |
| 6-4 | 21 min. | 8.9 | 1.062 | 0.144 | 0.300 | 0.6 | none | 10.5 | none | 2.5 | Falling heart |
| 7-2 | Recovery | 21.0 | 1.104 | 0.144 | 0.320 | 1.0 | none | 10.5 | none | 3.4 | Spoke within 15 secs. |

There were signs of approaching unconsciousness at the moment of ending the experiment, but F. spoke fifteen seconds after beginning to breathe pure air.

Protocol 4.—Pfc. T. H. K.; final oxygen, 7.1 per cent.; total time, 27 minutes, 9 seconds.

The clinical interest is in the partial collapse of the heart and fall of blood pressure without definite loss of consciousness. T. H. K. was a strong muscular type and was taken off because of beginning general clonic tremors. Muscular clonus lasted for 20 seconds, but he recovered control after the first few inspirations.

TABLE 5.—Pfc. T. H. K., March 9, 1919

Time of run 27 minutes, 9 seconds. Final oxygen, 7.15 per cent.

| Trace and Pulse No. | Time | Oxygen, per Cent. | Duration in Sec. | | | Amplitude in Mm. | | | | | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | R-R | P-R | R-T | P | Q | R | S | T | |
| 1-7 | Normal | 21.0 | 0.840 | 0.160 | 0.340 | 1.0 | none | 16.0 | none | 3.0 | Trembling |
| 2-5 | 5 min. | 18.4 | 0.868 | 0.168 | 0.360 | 1.0 | none | 16.5 | none | 3.5 | Sinus arrhythmia |
| 3-1 | 5 min. | 18.4 | 0.760 | 0.168 | 0.352 | 1.2 | none | 16.5 | none | 3.0 | |
| 3-2 | 10 min. | 15.9 | 0.696 | 0.168 | 0.332 | 1.6 | none | 15.5 | none | 2.4 | |
| 4-3 | 15 min. | 13.3 | 0.748 | 0.160 | 0.336 | 1.0 | none | 15.0 | none | 2.0 | Sinus arrhythmia |
| 4-6 | 15 min. | 13.3 | 0.672 | 0.160 | 0.336 | 1.3 | none | 16.0 | none | 2.0 | |
| 5-2 | 20 min. | 10.7 | 0.640 | 0.160 | 0.320 | 1.5 | none | 16.0 | none | 1.8 | |
| 6-2 | 22 min. | 9.7 | 0.576 | 0.152 | 0.300 | 1.6 | none | 16.0 | none | 1.6 | |
| 7-2 | 24 min. | 8.7 | 0.544 | 0.160 | 0.312 | 1.5 | 1.4 | 17.0 | none | 0.4± | T very flat |
| 8-7 | 26 min. | 7.7 | 0.548 | 0.148 | 0.300 | 1.5 | 2.0 | 16.0 | none | 0.4± | |
| 9 | Recovery* | | | | | | | | | | |

* See Table 6.

The systolic blood pressure remains constant to 8.2 per cent. oxygen, then drops suddenly and rapidly. The diastolic pressure also remains constant at 80 mm. to 9.7 per cent., then rapidly falls through five minutes to 44 mm. The heart rate of 80 per minute increased to 90 at the twenty-ninth minute then to 116 at the last reading. The electrocardiograms show that the rate

dropped through 63 to 55 and became very irregular (Plate 3, Figs. 9 and 10) during the interval between the last clinical pulse reading and the first recovery reading.

There were only slight changes in the electrocardiogram to the twenty-sixth minute. No important change in the conduction, and only very slight shortening of the R-T interval occurred as the usual augmentation of rate came on. A long tracing of thirty-two heart beats taken at the close of the

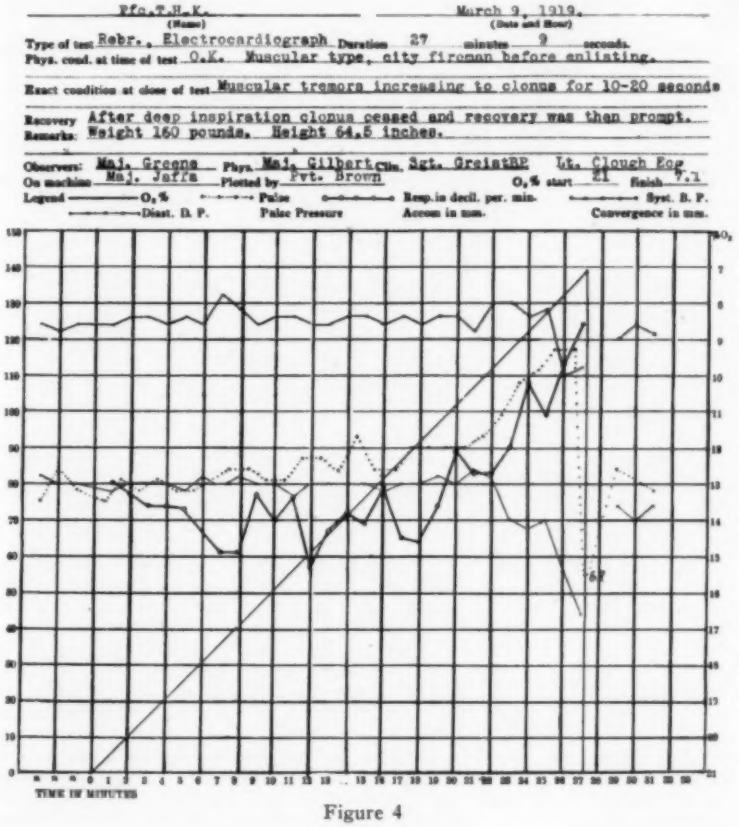
Pfc. T. H. K.
(Name)
March 9, 1919.
(Date and Hour)
Type of test Rebr., Electrocardiograph Duration 27 minutes 9 seconds.
Phys. cond. at time of test O.K. Muscular type, city fireman before enlisting.
Exact condition at close of test Muscular tremors increasing to clonus for 10-20 seconds
Recovery After deep inspiration clonus ceased and recovery was then prompt.
Remarks: Weight 160 pounds. Height 64.5 inches.
Observers: Maj. Greene Phys. Maj. Gilbert Clin. Sgt. GreistRP Lt. Clough Eng
On machine Maj. Jaffa Plotted by Pvt. Brown O2 % start 21 finish 7.1
Legend O2 % Pulse Resp. in decil. per. min. Syst. B. P.
Diast. B. P. Pulse Pressure Accom in mm. Convergence in mm.
6.7
TIME IN MINUTES

Figure 4

experiment and during the early recovery stage shows complete dissociation of the auricular and ventricular rhythms. Already at 7.7 per cent. oxygen the rate had slowed, though the sequence was still normal. In the unphotographed interval the pace making function of the S-A node slowed below the critical point of stimulus production in the A-V node and the nodes became independent. This is shown by the irregularity of the P-P interval, where it can be determined, and by the evidence of varying locus of stimulus production in the auricle as evidenced by both direct and inverted form and varying amplitudes of the P waves. In addition, we have the increase of cardiac muscle irritability as shown by two heterogenetic ventricular beats. In fact, this fea-

ture of the record suggests that of digitalis poisoning, or the type of hyperirritability observed in the electrocardiograms of experimental animals after chloroform.

TABLE 6.—Pfc. T. H. K., March 9, 1919

Time of run 27 minutes, 9 seconds. Final oxygen, 7.15 per cent.
Electrocardiogram, No. 9, taken during the early after or recovery period. No S wave during this record.

| Pulse | Duration in Seconds | | | | Amplitude in Mm. | | | Remarks |
|---|---|---|---|---|---|---|---|---|
| | R-R | P-R | R-T | P | Q | R | T | |
| 1 | 0.952 | 0.500 | 0.360 | −2.0 | none | 18.0 | 3.4 | |
| 2 | 0.528 | 0.620 | 0.340 | −2.0 | none | 19.0 | 3.0 | |
| 3 | 0.940 | 0.200 | 0.338 | −1.6 | 0.5 | 18.0 | 2.5 | |
| 4 | 0.944 | 0.100 | 0.340 | −2.0 | 0.5 | 18.5 | 1.5 | |
| 5 | 0.944 | 0.340 | 0.360 | +0.5 | 1.5 | 19.0 | 2.0 | |
| 6 | 0.752 | none | 0.360 | none | 0.5 | 20.0 | 2.0 | |
| 7 | 0.940 | 0.180 | 0.320 | +1.2 | 0.5 | 19.0 | 1.8 | |
| 8 | 0.504 | none | 0.360 | none | 1.0 | 20.0 | 2.0 | |
| 9 | 0.940 | 0.240 | 0.320 | +2.0 | none | 18.5 | 3.2 | |
| 10 | 0.968 | none | 0.360 | none | 1.0 | 18.5 | 3.2 | |
| 11 | 0.944 | −0.144* | 0.340 | none | 1.0 | 18.5 | 2.0 | * R-P |
| 12 | 0.528 | none | 0.320 | none | 1.0 | 18.0 | 0.5 | |
| 13 | 0.900 | 0.220 | 0.320 | −1.0 | none | 17.0 | 2.0 | |
| 14 | 0.960 | −0.050 | 0.360 | −2.0 | none | 20.0 | 3.0 | |
| 15 | 0.484 | none | 0.360 | none | none | 19.0 | 2.0 | −P superimposed on |
| 16 | 0.928 | 0.240 | 0.320 | +1.8 | none | 16.5 | 2.6 | the lower limb of R |
| 17 | 0.512 | none | 0.280 | none | none | 19.0 | 4.5 | |
| 18 | 0.948 | 0.240 | 0.320 | P+T | none | 17.0 | 2.0 | Combined +P and T |
| 19 | 0.480 | none | 0.300 | none | 0.5 | 19.0 | 3.5 | |
| 20 | 0.920 | 0.240 | 0.280 | −1.5 | none | 10.0 | ? | Ventricle complex ec- |
| 21 | 0.480 | none | 0.372 | none | 0.5 | 18.5 | 3.0 | topic |
| 22 | 0.824 | 0.320 | 0.380 | ? | none | 10.0 | 3.0 | |
| 23 | 1.080 | 0.064 | 0.348 | +1.0 | none | 17.0 | 3.0 | |
| 24 | 0.972 | 0.050 | 0.360 | +1.0 | none | 19.0 | 2.5 | |
| 25 | 0.472 | none | 0.360 | none | none | 19.0 | 3.0 | |
| 26 | 0.960 | 0.280 | 0.336 | −1 | none | 10.0 | 4.0 | |
| 27 | 1.000 | 0.100 | 0.360 | +1 | none | 18.0 | 2.0 | |
| 28 | 1.000 | −0.160 | 0.360 | +1 | 1 | 19.0 | 2.0 | |
| 29 | 0.488 | none | 0.360 | none | none | 18.5 | 2.8 | |
| 30 | 0.928 | 0.220 | 0.320 | +? | none | 16.5 | 2.5 | |
| 31 | 1.012 | 0.140 | 0.360 | +1 | 1 | 17.5 | 2.5 | |
| 32 | ..... | −0.140 | 0.360 | +1 | none | 16.0 | 2.2 | |

The physiologic and clinical chart is unique in several features. He reached 5.9 per cent. oxygen, an equivalent altitude of 31,500 feet. He made good compensations but not in the typical way. Instead of the usual early gradual cardiac acceleration beginning about the fifteenth minute, his heart rate ran very uniform until the last two minutes. The rate then augmented from 84 in the twenty-second to 150 in the twenty-fourth minute just before the close. The systolic pressure was over 150 mm. from the start but remained constant to the twelfth minute. From this time it increased steadily for eight minutes then sharply the last two minutes to a total of 194 mm. The diastolic pressure slowly increased until the very last minute when it suddenly broke 20 mm.

The effect of prolonged athletic activity is manifest in Sgt. M.'s excessive respiratory minute volume. This began at 17 liters in the first minute, dropped to just under 10 liters at 10 minutes, and increased rapidly after the seventeenth minute to the enormous volume of 26.8 liters during the twenty-third or last full minute. Compensations are due to augmentation of respiratory volume and of blood pressure. These meet the strain to 7 per cent. oxygen, when cardiac acceleration was added. At the moment of unconsciousness the break in diastolic pressure and in respiration had begun.

W. C. M. was physical director at Lakewood. He is a man of exceptional muscular development and physical endurance. There was a lively competition among the men at Lakewood in an attempt to exceed the record of Sgt. M. and the sergeant himself entered into the spirit of this competition. Notwithstanding the large volume of air breathed, he became very cyanotic during the last five minutes. The clinician did not terminate the test until the onset

of unconsciousness when the mouthpiece was instantly removed. Consciousness reappeared after the first inhalation of pure air. Reflex muscular control was not lost and the sergeant protested that he had not yet reached his limit.

The heart rate was very constant and the cardiograms show that there was no change in the P-R interval until the twentieth minute, and then only in the shorter beats of the arrhythmia periods. The R-T intervals became shorter

PROTOCOL 5.—Sgt. W. C. M.; final oxygen, 5.9 per cent.; total time, 23 minutes, 48 seconds.

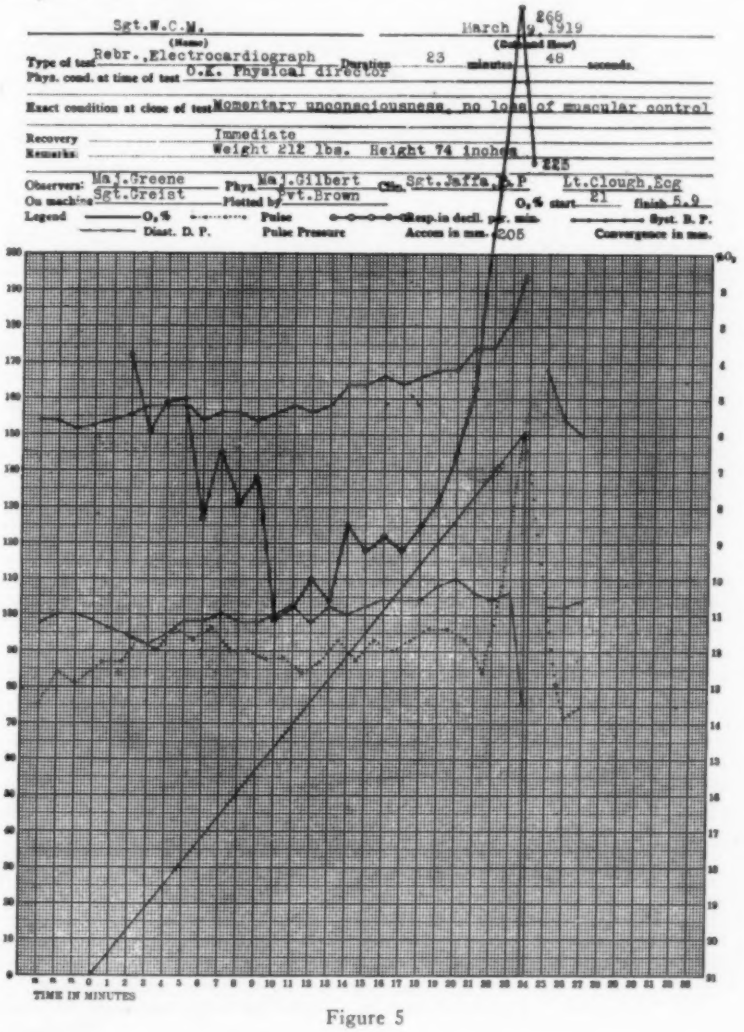


Figure 5

beginning at the twentieth minute. The character of the electrocardiogram was abnormal in only one feature. The R wave was short and bifurcated. The U wave was present in many of the cycles.

TABLE 7.—Sgt. W. C. M., March 10, 1919

Time of run 23 minutes, 48 seconds. Final oxygen, 5.9 per cent.

| Trace and Pulse No. | Time | Oxygen, per Cent. | Duration in Sec. | | | Amplitude in Mm. | | | | | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | R-R | P-R | R-T | P | Q | R | S | T | |
| 1-1 | Normal | 21.0 | 0.812 | 0.160 | 0.320 | 1.5 | none | 7.0 | none | 2.0 | Some sinus arrhythmia |
| 2-2 | 5 min. | 17.8 | 0.580 | 0.160 | 0.320 | 1.0 | tr. | 7.5 | none | 1.2 | Some sinus arrhythmia |
| 3-1 | 10 min. | 14.6 | 0.680 | 0.160 | 0.320 | 1.0 | none | 7.5 | none | 1.2 | |
| 4-2 | 15 min. | 11.5 | 0.680 | 0.160 | 0.320 | 0.8 | none | 7.5 | none | 1.0 | |
| 5a-1 | 20 min. | 8.3 | 0.656 | 0.160 | 0.312 | 0.8 | 0.6 | 7.0 | none | 1.0 | |
| 5b-3 | 20 min. | 8.3 | 0.632 | 0.144 | 0.300 | 0.8 | 1.0 | 6.5 | none | 1.0 | |
| 6-1 | 22 min. | 7.0 | 0.504 | 0.160 | 0.260 | 1.2 | 1.0 | 9.0 | none | 1.0 | |
| 2d from last | 22 min. | 7.0 | 0.468 | 0.136 | 0.256 | 1.0 | 2.0 | 7.0 | none | 0.6 | |
| 7-3 | Recovery | 21.0 | 0.700 | 0.144 | 0.300 | 1.0 | 1.0 | 7.0 | none | 1.6 | Momentary unconsciousness |
| Last pulse | Recovery | 21.0 | 0.740 | 0.100 | 0.292 | 0.6 | 1.0 | 8.0 | none | 2.0 | |

The stress of oxygen want on local cardiac mechanisms appears only in the recovery tracing which was taken at practically the moment of the removal of the mouthpiece (Plate 4, Fig. 8). The fifth beat in this figure shows a very slight negative P wave, the sixth beat has a well defined negative P. The inverted P continues through seven successive contractions. On the eighth, i. e., the twelfth beat of the figure, the negative wave is reduced in amount, and on the next beat the normal positive P appears and continues until the end of the photograph. During the period of inverted P waves the rate is reduced slightly as compared with the rate preceding and following the group, i. e., from 167 to 157, then back to 166 per minute. We consider this a splendid example of just beginning displacement of origin of the sino-auricular rhythm. The point of origin of the rhythm is evidently from a new source below, or from a lower point in the normal pace making center. It is the initial stage of the effect of oxygen want as affecting the reactions of the heart, in which the most advanced stages are represented by the terminal electrocardiograms of T. B. M. and D. W. O.

Protocol 6.—Sgt. T. B. M.; final oxygen, 7.6 per cent.; total time, 25 minutes, 54 seconds.

Sergeant T. B. M.'s physiologic and clinical chart shows poor compensations. His slow heart-rate in the late electrocardiograms is explained by the clinical collapse during the last two minutes of his test. The heart increased in rate beginning on the tenth minute and the increase amounts to about 25 beats during the last five minutes. It ends in an abrupt drop from a rate of 117 to 75 in the last minute. The electrocardiogram (Plate 5, Fig. 8), taken during the twenty-fifth minute (apparently later in the minute than the clinical rates recorded) shows the new slow rate, which had fallen to 62 per minute in the first beat photographed. In the early recovery period the rate varied from 61 to 64 and was fairly constant.

Although unconscious at the last, it is obvious that the heart rate was in itself adequate. The failure in compensation was due to the inadequate blood pressure. Both systolic and diastolic pressures fell from the beginning, but the fall was marked and more rapid after the eighteenth minute as the chart shows. Respiration also failed of adequate compensation. The highest minute

Sgt.T.B.M. (Name) March 10, 1919 (Date and Hour)

Type of test Rebr., Electrocardiograph Duration 25 minutes 54 seconds

Phys. cond. at time of test O.K.

Exact condition at close of test Unconscious, neck muscles relaxed, pale. Breathing slow and faint

Recovery Slow and gradual, breathing normal 26 sec., talked 96 sec

Remarks: Pale and perspiring 5 minutes later. Weight 134 lbs. Height 67 inches.

Observers: Maj.Greene Phys. Maj.Gilbert Clin. Sgt.Greist,R.F Lt.Clough,Ecg

On machine Sgt.Jaffa Plotted by Pvt.Brown $O_2$% start 21 finish 7.6

Legend ——— $O_2$% ·····• Pulse o-o-o-o Resp.in decil. per min. ——— Syst. B. P.

——— Diast. D. P. Pulse Pressure Accom in mm. Convergence in mm.

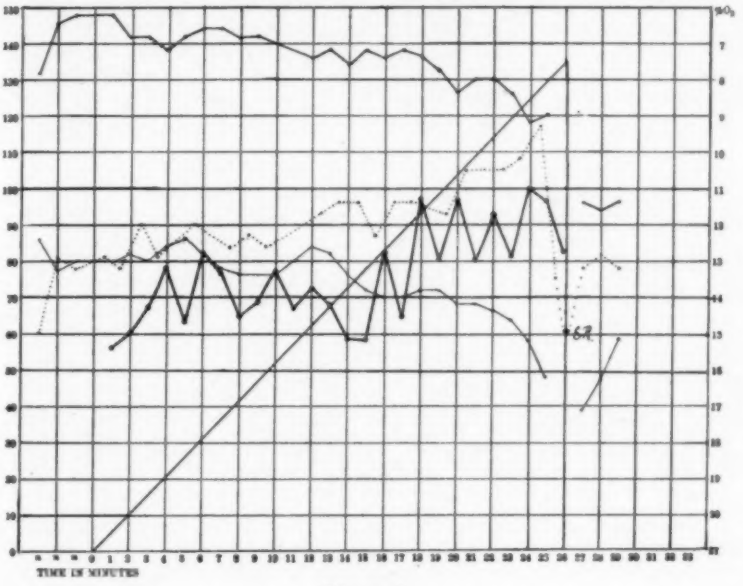


Figure 6

TABLE 8.—SGT. T. B. M., MARCH 11, 1919

Time of run 25 minutes, 54 seconds. Final oxygen, 7.6 per cent.

| Trace and Pulse No. | Time | Oxygen, per Cent. | Duration in Seconds | | | Amplitude in Mm. | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | R-R | P-R | R-T | P | Q | R | S | T |
| 1-1 | Normal | 21.0 | 0.852 | 0.140 | 0.340 | 1.0 | 1.0 | 18.5 | 2.5 | 3.2 |
| 2-1 | 5 min. | 18.4 | 0.760 | 0.132 | 0.328 | 1.0 | 1.0 | 19.0 | 2.5 | 2.0 |
| 3-1 | 10 min. | 15.9 | 0.652 | 0.144 | 0.320 | 1.0 | 1.0 | 19.0 | 3.0 | 1.5 |
| 3-11 | 10 min. | 15.9 | 0.840 | 0.140 | 0.320 | 1.0 | 1.0 | 20.0 | 2.5 | 2.5 |
| 4-10 | 15 min. | 13.3 | 0.520 | 0.132 | 0.280 | 2.0 | 1.5 | 19.0 | 1.0 | 1.5 |
| 4-1 | 15 min. | 13.3 | 0.672 | 0.140 | 0.340 | 1.4 | 2.0 | 20.0 | 2.0 | 1.4 |
| 5-4 | 20 min. | 10.7 | 0.530 | 0.132 | 0.308 | 1.3 | 1.0 | 18.0 | 2.0 | 1.0 |
| 5-11 | 20 min. | 10.7 | 0.696 | 0.148 | 0.280 | 1.0 | 1.0 | 20.0 | 2.0 | 1.0 |
| 6-15 | 22 min. | 9.6 | 0.604 | 0.128 | 0.312 | 2.0 | 2.5 | 19.0 | 3.0 | 1.0 |
| 6-1 | 22 min. | 9.6 | 0.628 | 0.136 | 0.300 | 2.0 | 1.5 | 21.0 | 3.0 | 1.0 |
| 7-5 | 24 min. | 8.6 | 0.472 | 0.120 | 0.272 | 1.5 | 1.0 | 18.0 | 2.0 | 0.4 |
| 7-1 | 24 min. | 8.6 | 0.512 | 0.132 | 0.320 | 2.0 | 2.0 | 19.0 | 2.5 | 0.5 |
| 8-1 | 25 min. | 8.1 | 0.944 | none | 0.320 | none | 1.4 | 19.0 | 2.0 | 2.0 |
| 9-1 | Recovery | 21.0 | 0.920 | 0.092 | 0.348 | 1.0 | 1.3 | 20.5 | 2.4 | 2.8 |

See Tables 9 and 10.

volume reached was only 10 liters. The whole clinical picture is that of a strong muscular type with nervous and circulatory apparatus adequate only to resist the effects of moderate reduction of oxygen. As 8 per cent. was approached, collapse of the peripheral vascular mechanism and of the heart occurred. Recovery was slow, due no doubt not so much to the heart as to the failure of the peripheral blood vessels to regain their tone, shown in the low diastolic pressure in the recovery period. Unconsciousness occurred in a few seconds short of twenty-six minutes. He recovered a degree of consciousness in twenty seconds but did not talk for one minute and ten seconds. He remained pale and perspired freely for several minutes.

The electrocardiograms show the usual progressive acceleration of pulse and decrease in the time of the cycle to the twenty-fourth minute. Conduction changed from 0.140 to 0.120 second at 8.6 per cent. oxygen. The R-T interval is also slightly decreased. Both these changes are well known functions of rate acceleration after exercise, etc. The amplitude of the deflections was constant, except for the diminution of the T wave, from 3.2 to 0.4 mm. in the twenty-fifth minute as final stage of the experiment, 8.1 per cent. oxygen.

TABLE 9.—Sgt. T. B. M., March 11, 1919

Time of run 25 minutes, 54 seconds. Final oxygen, 7.6 per cent.

| Trace No. 8 See Plate 5 | Duration in Seconds | | | Amplitude in Mm. | | | | |
|---|---|---|---|---|---|---|---|---|
| | R-R | P-R | R-T | P | Q | R | S | T |
| 1 | 0.944 | none | 0.320 | none | 1.4 | 19.0 | 2.0 | 2.0 |
| 2 | 0.944 | none | 0.300 | none | 1.0 | 19.0 | 2.0 | 2.0 |
| 3 | 0.952 | none | 0.320 | none | 1.0 | 18.0 | 1.5 | 2.0 |
| 4 | 0.936 | none | 0.320 | none | 1.0 | 19.0 | 2.0 | 2.0 |
| 5 | 0.948 | none | 0.312 | none | 1.2 | 21.0 | 1.5 | 1.6 |
| 6 | 0.948 | none | 0.320 | none | 1.0 | 21.0 | 1.0 | 2.2 |
| 7 | 0.952 | none | 0.320 | none | 1.0 | 19.0 | 2.0 | 2.0 |
| 8 | 0.948 | none | 0.320 | none | 1.0 | 18.0 | 2.0 | 2.5 |
| 9 | 0.940 | none | 0.304 | none | 1.3 | 21.0 | 2.0 | 2.0 |
| 10 | 0.944 | none | 0.320 | none | 1.0 | 18.0 | 2.0 | 2.3 |
| 11 | 0.948 | none | 0.300 | none | ... | 19.0 | 2.0 | 2.0 |
| 12 | 0.948 | none | 0.312 | none | 1.0 | 19.0 | 2.0 | 2.5 |
| 13 | 0.932 | none | 0.320 | none | 1.2 | 18.5 | 2.5 | 2.0 |

Profound changes occurred in the character of the terminal cardiogram, changes that do not disappear through the short recovery record obtained. The important fact is the entire disappearance of any evidence of the P wave. The loss of the P is associated with slowing of the pulse rate, from 128 to 63 per minute. In this period (Plate 5, Fig. 8) there is a record of fourteen ventricular complexes, nine of which are ideally recorded, but not one is introduced by any evidence of auricular activity. Not one of the nine is complicated by extraneous currents and all are regular and clean of type. Table 8 presents the measurements of all the complexes in Plate 5, Figure 8. The R's do not present amplitude changes that indicate inclusion of the P waves. It is evidently a rhythm of A-V nodal origin. The dissociation evidently occurred beween Figures 7 and 8 of Plate 5. We have no evidence recorded in the tracings of direct auricular action, versus inhibition, the possibilities of which we have considered in relation to the cause of the dissociation.

The condition shown in the tracing at the moment before the removal of the mouthpiece and the admission of pure air (Plate 5, Fig. 8), is carried over, in part, in the tracing immediately after the admission of pure air during the recovery tracing (Plate 5, Fig. 9). The rhythm does not yet begin in the S-A node, as shown by the inverted P and the short P-R interval; the first eight contractions show an inverted P wave; no P appears during the next five contractions, and an inverted P then reappears in the last three contractions. The first eight P-R intervals are progressively shorter, from 0.092 to 0.016

second. When they reappear after five beats, they become progressively longer, from 0.040 to 0.100 second. It suggests an origin of the auricular contraction from points progressively lower in the rhythmic system, until the P either merges in the R or disappears entirely. The P then reappears, showing that the source of the rhythm moves progressively back toward the normal pace-maker. These facts show that we have a lighter degree of interference with the mechanism here than that shown in Plate 5, Figure 8. The first inhalation of pure air gave enough oxygen to partially remove the effect of oxygen want which led to the loss of rhythmicity in the normal controlling center and released activity in a lower portion of the system, as indicated by the inverted P at the beginning of the tracing. In the interval before the next inhalation of fresh air there was return of the low oxygen level which again suppressed activity in the auricle, as indicated by the total disappearance of the P wave. The progressive type of recovery in the inverse direction was produced rapidly on the influx of oxygen following the next respiration. It shows the return of the pace-maker toward its normal location. If the record could have continued during a few more heart beats it would have revealed a complete and permanent recovery of the sino-auricular control.

TABLE 10.—Sgt. T. B. M., March 11, 1919

Time of run 25 minutes, 54 seconds. Final oxygen, 7.6 per cent. Trace No. 9, the recovery record while breathing pure air.

| Plate 5 Pulse | Duration in Seconds | | | Amplitude in Mm. | | | | | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| | R-R | P-R | R-T | P | Q | R | S | T | |
| 1 | 0.920 | 0.092 | 0.348 | —1.0 | 1.3 | 20.5 | 2.4 | 2.8 | |
| 2 | 0.920 | 0.096 | 0.360 | —1.0 | 1.5 | 19.0 | 2.5 | 3.5 | |
| 3 | 0.920 | 0.088 | 0.380 | —1.0 | 1.0 | 20.0 | 1.0 | 3.2 | |
| 4 | 0.928 | 0.088 | 0.360 | —1.0 | 1.0 | 22.0 | 1.5 | 3.2 | |
| 5 | 0.928 | 0.052 | 0.380 | —1.0 | 1.0 | 21.0 | 1.5 | 3.2 | |
| 6 | 0.928 | 0.048 | 0.372 | —0.8 | ? | 22.0 | 1.0 | 3.0 | |
| 7 | 0.928 | 0.024 | 0.376 | —1.0 ? | 2.0 | 22.0 | 2.0 | 3.2 | |
| 8 | 0.924 | 0.016 | 0.360 | ? | 2.0 | 21.0 | 2.0 | 3.5 | P and Q coincide |
| 9* | 0.928 | none | 0.360 | none | 1.6 | 19.0 | 2.0 | 3.5 | External negative wave through pulses 8, 9 and 10 |
| 10 | 0.928 | none | 0.360 | none | 1.5 | 20.0 | 2.0 | 3.5 | |
| 11 | 0.936 | none | 0.380 | none | 1.5 | 20.5 | 1.2 | 3.0 | |
| 12 | 0.928 | none | 0.380 | none | 2.0 | 21.0 | ? | ? | |
| 13 | 0.928 | none | 0.360 | none | 1.8 | 20.5 | 1.0 | 3.4 | |
| 14 | 0.928 | 0.040 | ? | —0.8 | 1.0 | 21.0 | 1.0 | ? | |
| 15 | 0.912 | 0.080 | 0.360 | —1.2 | 1.0 | 22.0 | 1.5 | 3.0 | |
| 16 | 0.900 | 0.100 | 0.352 | —1.0 | 1.5 | 20.0 | 2.0 | 3.0 | |

* P is negative in preceding beats, and absent or buried in R-S interval here. In the thirteenth P is added to Q; in the fourteenth it is present. P is negative in entire record.

Protocol 7.—Sgt. D. W. O.; final oxygen, 8.5 per cent.; total time, 25 minutes, 3 seconds.

The clinical chart of Sgt. D. W. O., Figure 7, shows that his respiratory and circulatory pre-crisis responses are noncompensating. There is a fall of diastolic blood pressure and an even systolic pressure until the critical oxygen limit is reached, then collapse occurs promptly. The initial heart rate is high and sustained with only the slightest acceleration during the test. The cardiogram taken in the last minute of the test shows a very slow heart, around 50 per minute. This and the fall of diastolic pressure explain the unconsciousness that occurred. The clinical sheet classifies D. W. O. in a group well known to the Medical Research Laboratory as the non-compensating type. These men endure the test to a certain limit without any apparent compensation, then, without premonition or warning they collapse completely, usually at a comparatively high oxygen level, though not universally so. The electrocardiogram gives new light on what occurs in the heart of this type at the critical moment of collapse.

Sgt. D. W. O. began the test with the high heart rate of 94 per minute and increased only to 108 during the twenty-five minutes. The usual falling off in the time of the R-T interval occurs, from 0.320 to 0.280 second. There

was also the usual decrease in the T wave. The contractions of the auricle were strong, an amplitude of from 2 to 2.6 mm. for the P wave which continued to 8.6 per cent. oxygen. The T wave was lower and broader in type than the average. As the oxygen want progressed, a sharp negative wave appeared at the terminal portion of the T.

Sgt. D. W. O. became unconscious at the crisis of the experiment, though he retained reflex control of his muscles and sat erect as if asleep. Only a

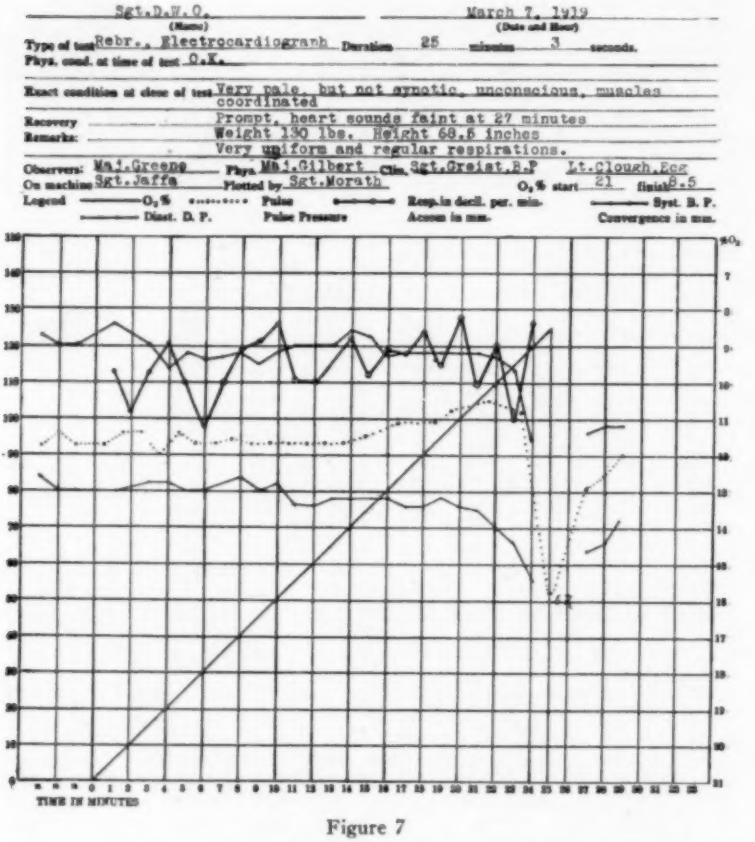
Sgt.D.W.O.
(Name)
March 7, 1919
(Date and Hour)
Type of test Rebr., Electrocardiograph Duration 25 minutes 3 seconds.
Phys. cond. at time of test O.K.
Exact condition at close of test Very pale, but not zynotic, unconscious, muscles coordinated
Recovery Prompt, heart sounds faint at 27 minutes
Remarks: Weight 130 lbs. Height 68.6 inches
Very uniform and regular respirations.
Observers: Maj.Greene Phys. Maj.Gilbert Clin. Sgt.Greist,R.P Lt.Clough,Ecg
On machine Sgt.Jaffe Plotted by Sgt.Morath O2 % start 21 finish 8.6
Legend O2 % Pulse Resp.in decil. per min. Syst. B. P.
Diast. B. P. Pulse Pressure Accom in mm. Convergence in mm.
TIME IN MINUTES

Figure 7

short tracing of seven ventricular contractions was obtained at this critical moment (Plate 6, Fig. 10), 8.5 per cent. oxygen. Reference to the electrocardiogram shows complete obliteration of the P wave and a strong well developed R-T and a weak T of the ventricular complex. Except for the strong R the electrocardiogram was as nearly iso-electric as in any experiment of the entire series. Plate 6, Figure 10 was made during the unconscious stage. The heart rate had dropped to 57 per minute and undoubtedly the circulation was very inadequate.

Recovery occurred promptly, as shown in Figure 11, Plate 6. There was a return of the P with normal amplitude and normal length of the P-R interval. The T slowly recovered its initial amplitude. The rate remained slower than at the beginning of the experiment but recuperated from the depressed rate at the close of the test.

TABLE 11.—Sgt. D. W. O., March 7, 1919

Time of run 25 minutes, 3 seconds. Final oxygen, 8.5 per cent.

| Trace and Pulse No. | Time | Oxygen, per Cent. | Duration in Seconds | | | Amplitude in Mm. | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | R-R | P-R | R-T | P | Q | R | S | T |
| 1-6 | Normal | 21.0 | 0.640 | 0.140 | 0.320 | 2.2 | 1.0 | 20.0 | 4.0 | 1.5 |
| 2-1 | 5 min. | 18.5 | 0.600 | 0.144 | 0.412 | 2.6 | 1.5 | 18.0 | 4.5 | 1.2 |
| 3-8 | 10 min. | 16.0 | 0.656 | 0.148 | 0.320 | 2.6 | 1.3 | 18.0 | 4.4 | 1.2 |
| 4-4 | 15 min. | 13.5 | 0.632 | 0.148 | 0.312 | 2.2 | 1.2 | 17.5 | 4.0 | 0.8 |
| 5 | 17 min. | 12.6 | 0.612 | 0.152 | 0.320 | 2.0 | 1.3 | 16.0 | 4.0 | 0.4 |
| 6 | 19 min. | 11.6 | 0.608 | 0.160 | 0.304 | 2.0 | 1.4 | 16.0 | 3.8 | 0.3 |
| 7 | 21 min. | 10.6 | 0.592 | 0.148 | 0.260 | 1.5 | 1.5 | 18.5 | 4.0 | +0.2 |
| 8 | 23 min. | 9.6 | 0.580 | 0.140 | 0.280 | 2.0 | 1.8 | 19.0 | 4.0 | −0.5 |
| 9 | 25 min. | 8.6 | 0.564 | 0.140 | 0.280 | 2.0 | 2.0 | 20.0 | 3.4 | −0.8 |
| 10-1 | 25 min. | 8.5 | 1.052 | none | 0.240 | none | 1.0 | 17.0 | 2.5 | 0.4 |
| 10-2 | | | 1.040 | none | 0.280 | none | 1.0 | 19.0 | 2.6 | 0.5 |
| 10-3 | | | 1.080 | none | 0.240 | none | 1.0 | 18.0 | 2.6 | 0.2 |
| 10-4 | | | 1.108 | none | ? | none | 0.8 | 17.0 | ? | none |
| 10-5 | | | 1.132 | none | 0.240 | none | 1.5 | 20.0 | 3.0 | |
| 10-6 | | | 1.140 | none | 0.260 | none | 0.5 | 18.0 | 2.5 | 0.3 |
| 11-2 | Recovery | 21.0 | 0.868 | 0.140 | 0.340 | 1.4 | 1.2 | 19.4 | 3.2 | 0.6 |

TABLE 12.—Summary of Cases with Electrocardiograms During the Low Oxygen Test

| Name | Time Min. | Time Sec. | Terminal Oxygen, per Cent. | Weight, Pounds | Height, Inches | Clinical Remarks |
|---|---|---|---|---|---|---|
| Pvt. N. W. A. | 21 | 40 | 9.7 | — | — | |
| Pfc. H. J. C. | 22 | 30 | 10.0 | 124 | 62 | Pale, no irregularities of the heart |
| Cpl. H. B. D. | 27 | 20 | 6.7 | 145 | 69 | Clonic muscular spasms, pale after 5 minutes |
| Cpl. F. J. D. | 24 | 26 | 8.1 | 150 | 70 | Cyanotic, not unconscious |
| Sgt. M. D. F. | 33 | 13 | 7.3 | 132 | 70 | |
| Pvt. J. F. | 21 | 56 | 8.4 | 132 | 68 | Very cyanotic, spoke in 15 seconds; N. C. A. case |
| Pfc. A. H. G. | 29 | 32 | 8.1 | 124 | 68 | |
| Pfc. T. H. K. | 27 | 9 | 7.1 | 160 | 64 | Called off at beginning of muscular tremors; clonus severe for 20 seconds; prompt recovery after deep inspiration |
| Sgt. H. K. | 30 | 27 | 6.5 | 140 | 67 | Expert diver |
| Cpl. W. D. L. | 29 | 13 | 6.9 | 143 | 69 | Clinical history of premature ventriculars, none during test; conscious to end |
| Sgt. W. C. M. | 23 | 48 | 5.9 | 212 | 73 | Momentary unconsciousness at end |
| Sgt. T. B. M. | 25 | 54 | 7.6 | 134 | 67 | Unconscious, muscles of neck relaxed, recovered in 26 seconds, talked in 96 seconds, pale drowsy and perspiring 5 minutes later |
| Sgt. E. O. McC. | 23 | 5 | 8.3 | 166 | 71 | |
| Pfc. A. H. McD. | 24 | 15 | 7.5 | 128 | 65 | |
| Sgt. D. W. O. | 25 | 3 | 8.5 | 150 | 68 | Unconscious at end, but retained reflex control of muscles, prompt recovery |
| Sgt. N. S. P. | 34 | 12 | 6.7 | 138 | 70 | |
| Sgt. F. J. P. | 28 | 2 | 8.8 | 130 | 68 | |
| Sgt. W. A. R. | 22 | 50 | 10.5 | 146 | 62 | Dazed if not unconscious at end, pale after 3 minutes |
| Sgt. B. S. | 24 | | 10.8 | 135 | 68 | Extreme arrhythmia |
| Cpl. L. D. S. | 20 | 30 | 1.09 | — | — | |
| Pvt. W. V. T. | 24 | 9 | 8.1 | 135 | 69 | |

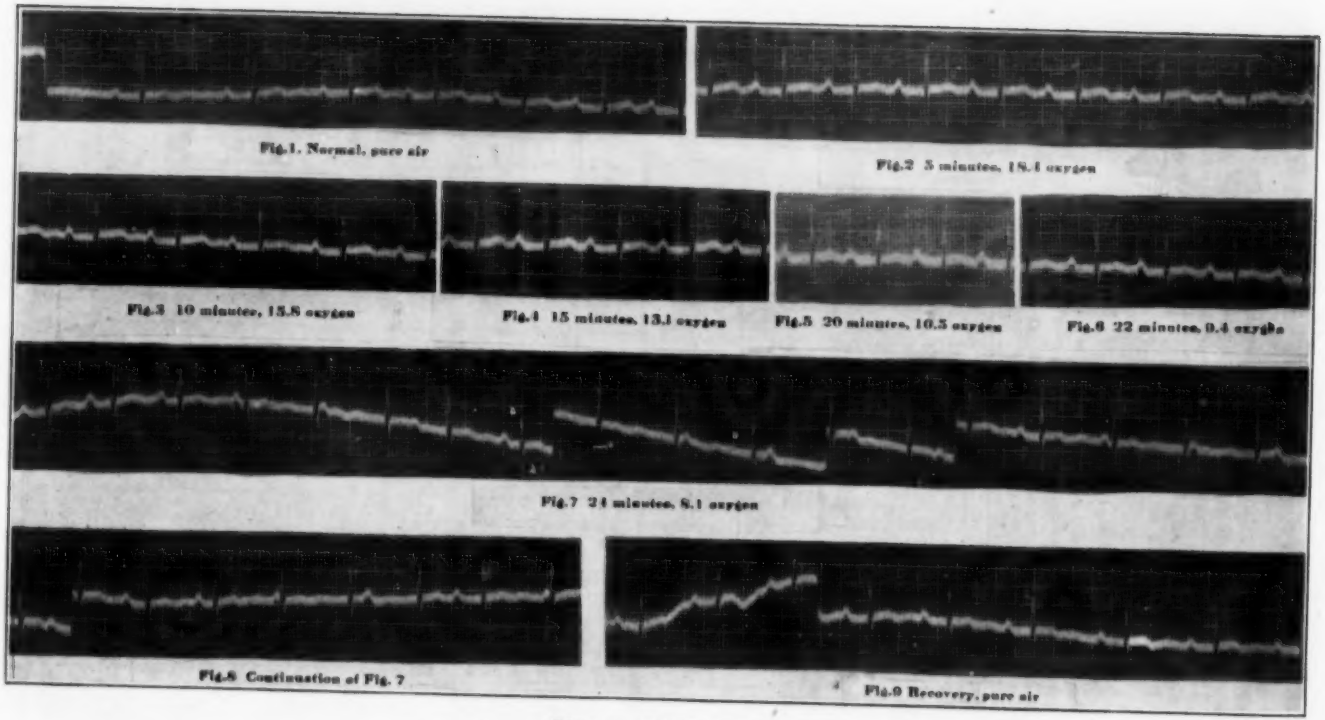

Fig.1. Normal, pure air

Fig.2 5 minutes, 18.4 oxygen

Fig.3 10 minutes, 15.8 oxygen

Fig.4 15 minutes, 13.1 oxygen

Fig.5 20 minutes, 10.5 oxygen

Fig.6 22 minutes, 9.4 oxygen

Fig.7 24 minutes, 8.1 oxygen

Fig.8 Continuation of Fig. 7

Fig.9 Recovery, pure air

Plate 1. Cpl. F. J. D.

### CHANGES IN THE TYPE OF THE ELECTROCARDIOGRAM WITH THE ONSET OF OXYGEN WANT

*Comparison of Cases.*—The effects of extreme low oxygen in the air breathed expressed in the electrocardiograms of our twenty-one men are varied and extreme. The degree of oxygen want endured by the majority, thirteen cases, without visible deleterious effects on the heart, is surprising. At least ten of the men reached 10 per cent. oxygen and less with no drastic changes in the electrocardiograms. Of these, five ran to 8 per cent. oxygen and two to less than 7 per cent. The series illustrates the fact established by the general experience of the Medical Research Laboratory that the limit of endurance to low oxygen covers the rather extreme range of from 6 per cent. or less to 10 per cent. and more among vigorous and well developed apparently normal individuals. The men in the series reported now were tested to as low as 5.9 per cent., and taken off at as high as 10.9 per cent.

Seven of the twenty-one men show disturbances of normal heart function, varying from slight and evanescent changes to the most profound and vital interference with normal rhythm and conduction. The extreme changes occurred at the crises of low oxygen, H. B. D., 6.7 per cent.; F. J. D., 8.1 per cent.; J. F., 8.4 per cent.; T. H. K., 7.1 per cent.; W. C. M., 5.9 per cent.; T. B. M., 7.6 per cent.; and D. W. O., 8.5 per cent. Two of the seven had severe clonic muscular spasms which tended to mask symptoms which are the usual signs of impending loss of consciousness. The one clear case in which unconsciousness was not reached out of the seven showing heart irregularities, was that of F. J. D. at 8.1 per cent. oxygen. He developed complete dissociation but with persistence of rather regular auricular and ventricular rhythms. Four of the seven men with extreme heart irregularity were clearly unconscious. In one W. C. M., at 5.9 per cent., the unconscious stage was brief and momentary only, as was also the heart irregularity (Table 3, Plate 10, Fig 8). In the remaining three the cardiac disturbances were more profound, as was also the general evidence of oxygen asphyxiation of the nervous system.

Even casual examination shows that circulatory changes during the rebreather test are slight during the first two thirds of the test. In the last third, the changes come on rapidly until the onset of what we have called the crisis. If the test is pushed still further unconsciousness occurs. Then the disturbances of the heart are rapid, profound, and vital. Twenty seconds at this crisis may suffice to drop the heart rate from its maximum compensating high rate to the profound condition of dissociation observed in F. J. D., or the suppressed auricular beats and slow rhythm of D. W. O. The details are further

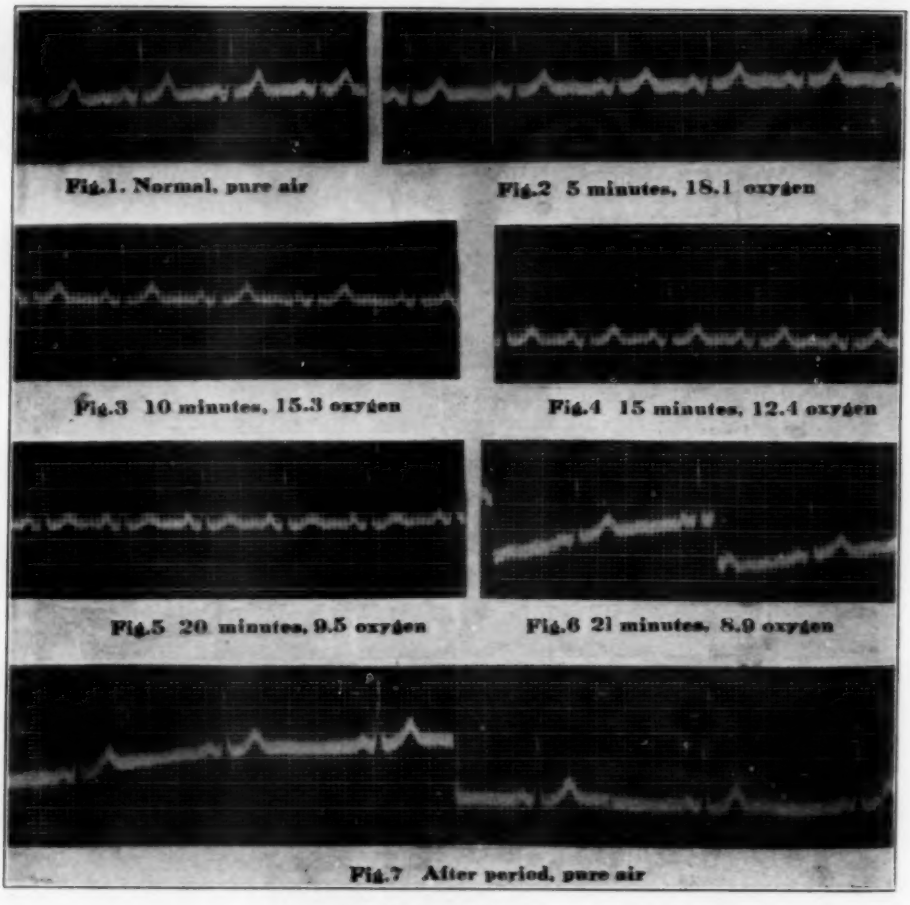

Fig.1. Normal, pure air

Fig.2 5 minutes, 18.1 oxygen

Fig.3 10 minutes, 15.3 oxygen

Fig.4 15 minutes, 12.4 oxygen

Fig.5 20 minutes, 9.5 oxygen

Fig.6 21 minutes, 8.9 oxygen

Fig.7 After period, pure air

Plate 2. Pvt. J. Y.

discussed under two headings, one presenting the general precrisis changes leading up to the crisis or crest of the compensating adjustments, and the other postcrisis and intrinsic changes at and following the crisis.

### GENERAL OR PRECRISIS CHANGES IN THE TYPE OF THE ELECTROCARDIOGRAM

The primary changes in the general type of the electrocardiogram with the onset of low oxygen are not pronounced and not uniformly constant. A fair proportion (nine cases) show decrease in the time of the conduction, thirteen show corresponding decrease in the time of the ventricular complex with acceleration of rate; two cases show no change, and all show decrease in the amplitude of the T wave. There is no constant association of the change in total time of the conduction and the duration of the ventricular complex in the same individual though association is the rule. The length of the P-R interval is only very slightly influenced by oxygen want up to the crisis, i. e., until the onset of unconsciousness is imminent. There is an appreciable acceleration of the P-R interval at the lower oxygen levels. This amounts in H. J. C. to 6 per cent. acceleration, N. S. F. 12, T. B. M. 7 per cent., etc. These decreases of from 6 to 12 per cent. in conduction time are representative. It is by no means a constant phenomenon. This is not a direct cardiac effect of low oxygen. It is probably bound up in the factors which cause the acceleration in rate. The stimulus that augments the pace making process also hastens conduction.

The R-T interval, or ventricular complex, is also slightly shortened before the crisis is reached. In H. B. D. the normal R-T of 0.320 seconds is reduced to 0.300 and 0.292 seconds in the twentieth minute, 9.5 per cent. oxygen. It is 0.300 seconds in the twenty-seventh minute, 6.8 per cent. oxygen, and promptly returns to 0.320 seconds on breathing pure air. This recovery of the normal time of heart muscle contraction takes place even before the normal S-A rate is re-established in control of the rhythm. The change in contraction time is not profound. It amounts in the case of T. F. K. to a drop of from 0.340 second in the normal to 0.300 second in the twenty-sixth minute at 7.7 per cent. oxygen. This record shows an augmentation in the R-T interval at the fifth minute. However, the low T wave and the occasional uncertainty of its exact termination in Lead II compels us to lay less stress on the slight differences as they appear in tabulation.

In the case of H. K. the electrocardiogram is clear cut and the measurements are more accurate. The table shows a very regular shortening in the R-T with the decrease in oxygen. H. K. was

taken off while still giving normal general reactions. His R-T intervals in the first, fifth and fourteenth contractions of the recovery record are 0.280, 0.300 and 0.320 second, respectively. This is a very prompt and definite return to the original normal. The precrisis decrease in R-T time is coincident with the accelerated rate, and is doubtless due to the same reactive changes. Acceleration in heart rate is primarily at the expense of the quiescent phase of the cycle. This is approximately the iso-electric phase between the T and P waves. Our measurements show that *during the acceleration of rate produced by oxygen want the cardiac processes both of conduction and contraction are hastened.* The acceleration of conduction amounts to from 6 to 12 per cent. and more, and of contraction from 8 to 12 per cent., while the rate is accelerated by from 30 to 70 per cent.

A constant change observed throughout the series is in the character and amplitude of the T wave. The T decreased with low oxygen to the point of complete obliteration in some cases but always by from 50 to 75 per cent. of the amplitude of the normal. The chief change in the T is a simple diminution of amplitude. However, the type form of the complex is also altered. The normal T in Lead II, used by us throughout, is a positive deflection. It is developed slowly and is a symmetrical curve. As extreme oxygen want approaches it becomes much flatter in the positive phase and more abrupt in the negative phase. Or the deflection may be delayed until the very end of the R-T interval. In a few cases the T wave was terminal, slight in amplitude and sharply diphasic, i. e., a short positive followed by an abrupt and short negative, as in the case of D. W. O. (Plate 6, Figs. 8 and 9).

### CARDIAC CHANGES DURING THE POSTCRISIS OF OXYGEN WANT

The changes in the heart at and following the crisis of oxygen want occur rapidly and are retrogressive in character. The simplest and least complicated change of this type is the development of complete heart block (Cpl. T. J. D). This heart had a history of block. At the time of the test conduction was regular but slow, 0.32 second as against the normal average of from 0.12 to 0.16 second. At 8.1 per cent. oxygen, complete block abruptly developed. The critical period of onset is fortunately recorded in the electrocardiogram, (Plate I, Figs. 7 and 8). Dissociation persisted for the remainder of the test, and, what is of the greatest importance, disappeared promptly on breathing pure air. The weakest link in this heart is the conducting system. The dissociation is definite evidence that *during extreme oxygen want in man the process of conduction in the cardiac conducting system is suppressed.*

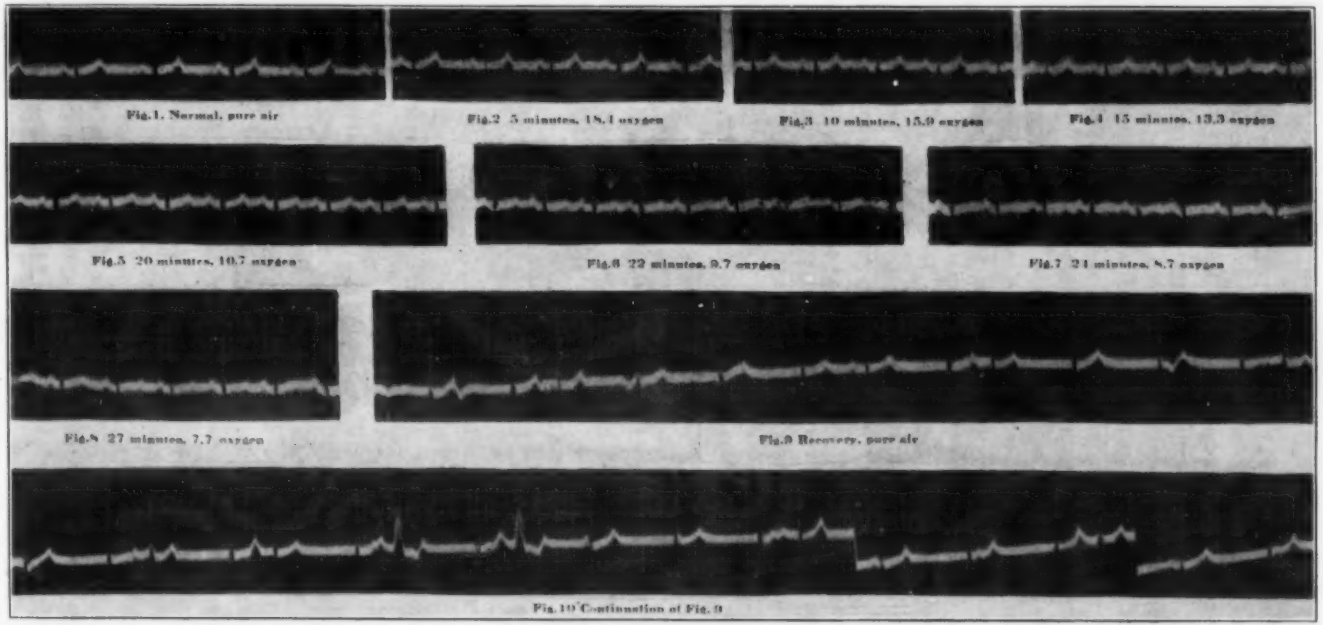
Fig.1. Normal, pure air
Fig.2 5 minutes, 18.1 oxygen
Fig.3 10 minutes, 15.9 oxygen
Fig.4 15 minutes, 13.3 oxygen
Fig.5 20 minutes, 10.7 oxygen
Fig.6 22 minutes, 9.7 oxygen
Fig.7 24 minutes, 8.7 oxygen
Fig.8 27 minutes, 7.7 oxygen
Fig.9 Recovery, pure air
Fig.10 Continuation of Fig. 9

Plate 3. Pfc. T. H. K.

This test developed the unusual phenomenon of a dissociated heart rhythm in which the auricular rate was slower than the ventricular. The P wave is clearly traceable and well defined, except for two evident buried beats. The ventricular complexes are A-V nodal types. The suppression of conduction in the internodal tissue makes possible the comparison of the two pacemaking centers under identical conditions during oxygen want. The P waves that occur are of the normal erect S-A type during the entire time of dissociation.

The P wave was suppressed in H. B. D. during the twenty-seventh minute, 6.8 per cent. oxygen. The P was absent for the first three beats of his recovery tracing, but the rest of the electrocardiogram shows complete recovery. This is a simple and uncomplicated case of disappearance of the pace-making function of the sino-auricular node with rhythm from the A-V node.

However, the very best illustration of disappearance of auricular rhythm is that of Sgt. T. B. M. At 8.1 per cent oxygen a long series of ventricular complexes occur without a vestige of the P wave. The protocol states the fact that nine ventricular complexes are ideally recorded in which the evidence is clear cut and decisive (Plate 5, Fig. 8).

The momentary partial recovery of an inverted P, and its subsequent loss and second re-establishment, shown in Sgt. T. B. M.'s recovery tracing, gives confirmation of the fact that *there are two fundamental effects that follow oxygen inadequacy, i. e., suppression of rhythm production in the S-A node and block in the internodal conducting tissue. These may occur together or independently.*

An inverted P for a few homogenetic beats followed by its disappearance in T. B. M. is produced wholly by oxygen want. The cardiac complex at this moment is just trembling on the threshold of functional capability, a little less oxygen and it fails completely to function, a little more and it functions normally. It is exactly the phenomenon observed in Sgt. W. C. M. at the corresponding stage. In the latter only the stage of an inverted P and a foreshortened P-R was reached. In the former the record catches the shift in the point of origin of the beat just at the extreme displacement reached by Sgt. W. C. M. and carries the change to the degree of complete suppression of function of all rhythmic tissue above the A-V node. In both instances the complete cycle from the initial state through that of depressed functional activity back to the original was photographed in the electrocardiograms and is presented in the corresponding figures. The actual measurements are given in Tables 9 and 10.

The displacement of the locus of rhythm production is shown in the shortening P-R intervals before the disappearance of the P wave, and by the corresponding increase in the P-R interval during the recovery stages of Sgt. T. B. M.

The complete suppression of function of the sino-auricular node is shown in Plate 6, Fig. 10, at the stage of 8.5 per cent. oxygen in the test of Sgt. D. W. O. This electrocardiogram shows as nearly complete suppression of heart function as one feels safe in producing in man. The rate is slow, about 51 compared with a rate of 83 a few moments earlier. The T is low and flat and the P wave cannot be detected.

The mechanism of the progressive acceleration of the heart during the precrisis period, has not been demonstrated. Evidence appears in our experiments showing that the inhibitory effects through vagus action are slightly increased between the five and fifteen minute stages but are reduced later. This last deduction is justified by the progressive decrease in sinus arrhythmia during the stage of marked acceleration. If the vagus center is responsible for the slow heart rate in the postcrisis stage it must become suddenly and excessively active just when the respiratory center ceases to function. The recovery of sequence contractions with the P wave of normal type but of reduced amplitude, and the P-R interval of normal duration promptly takes place in the after period. The facts seem clear that in man *the slowed rate and suppressed P wave are indicative of suppression of the pace making function of the sino-auricular node and the assumption of that function by the auriculo-ventricular node.* Whether this is due to direct oxygen want on the cardiac tissue itself in man, or is an indirect effect leading to vagospasm in the postcrisis period we cannot at present say. The human observations are not determinative though animal experimentation since the time of Klug indicates that vagospasm is the immediate cause of heart slowing at the crisis of systemic asphyxiation in the presence of carbon dioxid excess.

The terminal electrocardiograms of T. W. K. are of a very much more complicated type. The initial record is normal in type. Only the usual changes in conduction, amplitude and form of the T wave occur through to the 7.7 per cent. oxygen stage, i. e., almost to the end at 7.1 per cent. oxygen. In the tracing during the after period, started apparently before recovery occurred, there is profound upset in the reactions of the intrinsic cardiac mechanism. Heart block is clearly shown. The P wave is present in portions of the record but irregularly spaced and often inverted. The auricular rate, as in F. J. D., is slower than the ventricular rate. There is no P wave in relation to many of the ventricular complexes. If buried in the complex it cannot be shown. Two contractions of muscular origin complicate the irregularity. These facts are easily understood on the theory of suppression of function of the conducting tissue and retention of independent rhythm production in the sino-auricular node or its

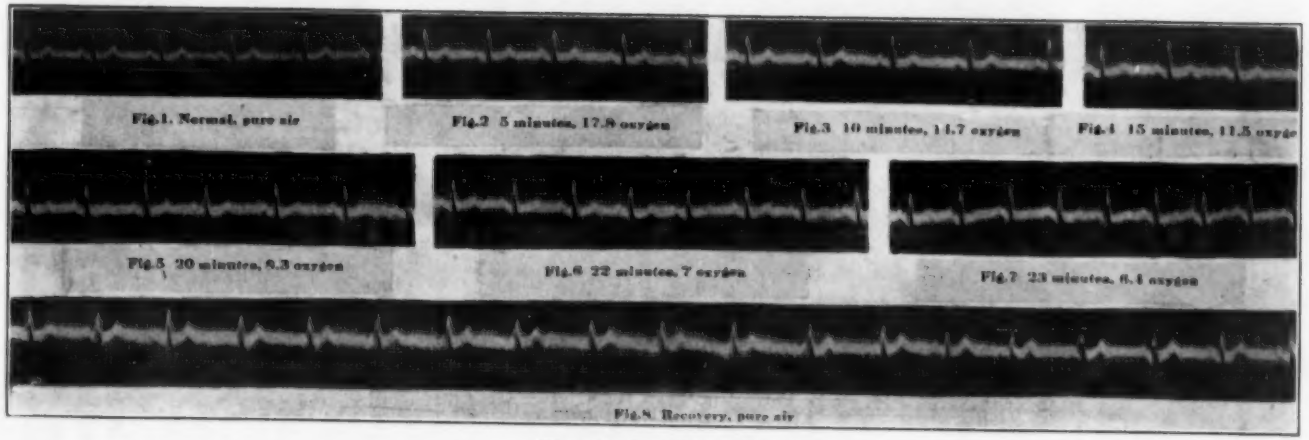
Fig.1. Normal, pure air
Fig.2 5 minutes, 17.8 oxygen
Fig.3 10 minutes, 14.7 oxygen
Fig.4 15 minutes, 11.5 oxyge
Fig.5 20 minutes, 9.3 oxygen
Fig.6 22 minutes, 7 oxygen
Fig.7 23 minutes, 6.4 oxygen
Fig.8. Recovery, pure air

Plate 4. Sgt. W. C. M.

vicinity, coincident with the erect P waves, but auriculoventricular or at least atrial dominant rhythm during the inverted P waves.

### DISCUSSION OF THE LITERATURE

We do not find any references in the literature dealing with the electrocardiographic method applied to the normal human during anoxemia. The nearest approach to the subject is in the very few cases photographed during the agonal stages of death in which the great excess of carbon dioxid is obvious.

The latest of this type is the study by Halsey [14] of a case of bronchopneumonia. Halsey secured a series of electrocardiograms through to the termination in ventricular fibrillation. His Figure 4 is more or less typical of a heart embarrassed but still beating with a normal sequential rhythm. The halving of the rate and of conduction time, that is "double the time in the earlier record," has never occurred in our tests. Whatever happens to the rate there has never been a multiple lengthening of the conducting time of this type. The unexpected phenomenon shown in Halsey's case is the great slowing of conduction with at the same time maintenance of a strong P wave. The phenomenon is not typical of anoxemia. In our experiments the carbon dioxid was removed but it is certainly present in excess in the dying heart in pneumonia. The gap between Halsey's Figures 5 and 6 is unfortunate, since it is evident that the P waves ceased during the time of that gap in which he has lost the record of the most crucial transitional change in function. The single P in the fourth beat of Figure 6 suggests that Halsey is dealing in this figure with suppression of the S-A nodal rhythm, i. e. by asphyxiation with or without complications.

Robinson [15] made electrocardiographic studies of the mode of death of the human heart. Four out of seven cases showed ventricular activity from 1.5 to 18 minutes after evidence of auricular activity had ceased. Two auricles outlasted the ventricles. In one case the auricle and ventricle stopped together. In three cases complete dissociation occurred. In five cases there was some delay in the conduction. In two cases the auricles ceased before there was any evidence of impaired conduction. There was always a marked slowing during independent ventricular rhythm, the ventricle contracting from fourteen to forty-seven times per minute. There was no auricular but one ventricular fibrillation. He observed interference with both rhythm and conduction, though his published records do not show the onset of the changes in the symptoms. The slowing of the ventricular rates observed by Robinson are confirmed by the slowing obtained by us

14. Halsey: Heart **6**:67, 1915.
15. Robinson: J. Exper. M. **16**:291, 1912.

when the evidence of auricular contraction disappears. Our rates are at a higher level, but we have not carried the degree of oxygen want to the extreme represented by a heart in the agonal stage during death from infectious disease.

Eyster and Meek [16] produced displacement of the pacemaking function from the S-A node to the A-V node by cooling, by anatomic isolation, by crushing, and by applying chemicals to the S-A node. Their evidence was that rhythm under these conditions never arises outside the parts of the heart containing specialized tissue. The origin of the rhythm is driven down to the atrial node or the A-V node.

Lewis and co-workers in investigations on the lower mammals have shown that both the S-A rhythm and the conduction can be delayed and even suppressed. Lewis [17] also used local cooling to study the development of the displaced beat. Cooling of the S-A node is followed by slowing of the rhythm. His electrocardiograms show that the new center of rhythm production is in the A-V node. Cooling may also interfere with nerve conduction.

Meakins [18] says that "the new rhythm has its origin some distance above the division of the main stem of the auriculo-ventricular bundle." He was able to produce ventricular forward block in the dog by compressing the bundle with a specially devised heart clamp applied after the establishment of A-V rhythm by cooling.

Lewis and Cotton [19] determined an almost constant acceleration of conduction in man as an immediate effect of exercise sufficiently strenuous to produce a considerable acceleration of the heart rate and labored breathing. Such acceleration of conduction does not occur when the acceleration of rate is induced by direct stimulation of the auricles by the application of induction shocks, a fact previously shown by Lewis and Oppenheimer.[20]

Acceleration of conduction would seem to be a function of the reactions of the accelerator nerve induced by the stimulus of exercise, or in our tests by the conditions of reduced oxygen. Lewis and Cotton's conduction time was accelerated by from 0.01 to 0.03 second. Their normal conductions were re-established in from three to five minutes and before the normal rates were re-established. Similar changes in conduction time have been observed in patients from exercise. Our highest acceleration in conduction was 0.048 second. The accelerations in rate which we observed all occurred in the precrisis period, and it was during this time that conduction was quickened.

16. Eyster and Meek: Heart **5**: 119, 227, 1914.
17. Lewis: Heart **5**:247, 1914.
18. Meakins: Heart **5**:281, 1914.
19. Lewis and Cotton: J. Physiol. **46**:60, 1913.
20. Lewis and Oppenheimer: Quart. J. M. **4**:145, 1910.

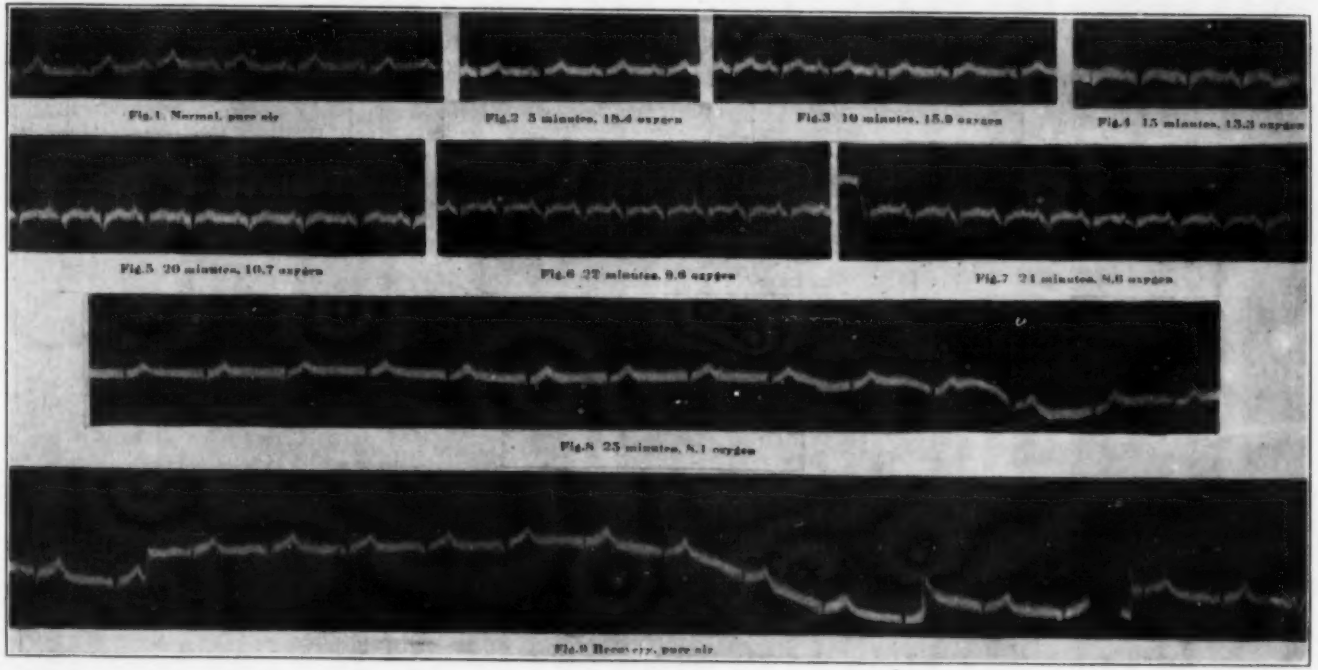
Fig.1. Normal, pure air
Fig.2 5 minutes, 18.4 oxygen
Fig.3 10 minutes, 15.9 oxygen
Fig.4 15 minutes, 13.3 oxygen
Fig.5 20 minutes, 10.7 oxygen
Fig.6 22 minutes, 9.6 oxygen
Fig.7 24 minutes, 8.6 oxygen
Fig.8 25 minutes, 8.1 oxygen
Fig.9 Recovery, pure air

Plate 5. Sgt. T. B. M.

The shorter P-R intervals observed by us at or after the crisis are associated with and explained by the displaced locus of rhythm production and are not accelerated conduction but shortening of the path.

Cohn [21] restudied the physiology of the cardiac vagus pathways showing that the right and left vagi, in dogs at least, do not exercise the same influence on the heart. The right vagus usually exerts a greater control over stimulus production while the left has a profound effect on conduction. Rothberger and Winterberg [22] had suggested earlier that the right vagus and cardiac accelerator nerves are distributed mainly to the S-A node and the left to the A-V node. Cohn and Lewis [23] examined the influence of the vagi in delaying conduction and in producing heart block. They showed that the left vagus usually had the greater effect on conduction, but that the difference was quantitative rather than qualitative. Lewis [17] showed that when the A-V rhythm controls the beat the vagus then acts at the A-V node and its vicinity to produce reversed block. The point is used by Lewis to support the inference that the vagus acts differentially on the conducting tissue above the A-V node. He also observed that in complete heart block in the cat the auricular rhythm of S-A origin completely drops out on deep asphyxiation, a point strictly comparable to our extreme cases of T. B. M. and D. W. O.

Eyster and Meek [24] present electrocardiograms of the disordered action of the heart produced by morphin. Auricular systoles are slowed and even suppressed, or the conduction is partially or completely blocked. Cohn [25] found that after the administration of morphin conduction was blocked and sometimes reversed, as shown by R-P intervals. He asserts that inhibition is the primary picture of morphin action if the right vagus only is intact, while disturbances of conduction predominate with intact left vagus. Cohn states that there is complete parallelism between morphin disturbances and right or left vagal stimulation, and that the heart is released from morphin by atropin or by freezing the vagus. Wilson [26] has shown that the A-V rhythm can be induced readily by vagus stimulation during the early stages of the action of atropin in young people, from eight to fifteen minutes. The A-V rhythm appeared spontaneously in three cases. A-V rhythm could not be induced in his normal cases before atropin was given, or after its maximal effects appeared. It was observed in two cases

21. Cohn: J. Exper. M. **16**:732, 1912.
22. Rothberger and Winterberg: Arch. f. d. ges. Physiol. **135**:559, 1910; **141**:343, 1911.
23. Cohn and Lewis: J. Exper. M. **18**:739, 1913.
24. Eyster and Meek: Heart **4**:59, 1912.
25. Cohn: J. Exper. M. **18**:715, 1913.
26. Wilson: Arch. Int. Med. **16**:989 (Dec.) 1915.

of cardiac disease. These records are of peculiar value and interest in that figures are given of simultaneous venograms that show coincidence of As and Vs waves with electrocardiograms under the initial atropin vagus stimulation. The electrocardiograms alone give no evidence of the P wave (Wilson's Fig. 4, A-V rhythm of Type 2).

Robinson and Auer [27] state in their papers on anaphylactic shock that marked changes occurred in heart activity in twenty-two out of twenty-four anaphylactic rabbits, whether the vagi were cut or not. In the dog "These cardiac changes consist of disturbances in conduction of the heart impulses, abnormalities in the ventricular contractions, and other unusual disturbances of the mechanism of the heart beat." They find inversion of the P wave, shortening of the P-R interval showing displacement of the pacemaker, and varying degrees of dissociation. The relationship between auricular and ventricular activity becomes disturbed "as shown by the abnormal proximity of the P and R waves (Fig. 15)." Their figure shows a P-R of 0.033 as against the pre-experimental time of 0.08 second. They say "it probably represents a change at the point at which the stimulus of the heart arises." This general picture coincides very well with the observed changes in our charts for T. B. M., D. W. O., and J. D., also for W. C. M. Robinson and Auer interpret the changes in the form of the ventricular complex in anaphylaxis as peripheral and local. The anaphylactic results are equally well explained on the hypothesis of vagal stimulation.

Lewis, White and Meakins [28] studied the effects of asphyxiation on conduction in the heart of the cat by the method of first cooling the S-A node and then allowing asphyxiation to develop by stopping artificial respiration, also by the method of simple asphyxiation without cooling. These methods make possible the study of asphyxial effects on conduction during the normal S-A rhythm in contrast with the type of rhythm of A-V origin. Their facts are developed by splendidly executed electrocardiograms. The conclusions emphasized by the authors are "(1) Asphyxia produces a gradually increasing *forward* heart block in the cat's heart beating from the S-A node. (2) It produces a gradually increasing *reversed* heart block when the heart chambers respond to the A-V node. (3) The main defect is in the portion of the functional system lying at a higher level (nearer the auricle) than the actual seat of impulse discharge in the A-V rhythm. (4) The A-V node or tissue in its immediate vicinity is the most susceptible tissue in respect of changes in the A-V conduction. (5) In the cat, so asphyxiated that there is a complete functional break between A-V node and auricle, the application of cold to the S-A

27. Robinson and Auer: J. Exper. M. **18**:556, 1913.
28. Lewis, White and Meakins: Heart **5**:289, 1914.

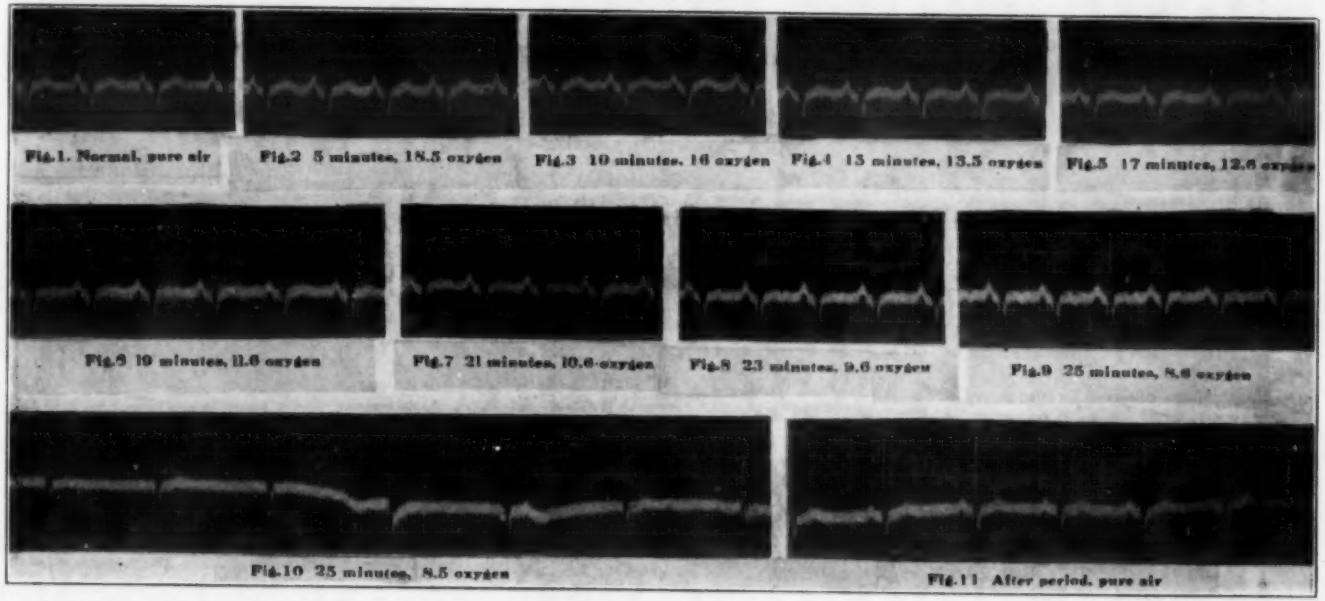
Fig.1. Normal, pure air
Fig.2 5 minutes, 18.5 oxygen
Fig.3 10 minutes. 16 oxygen
Fig.4 15 minutes, 13.5 oxygen
Fig.5 17 minutes, 12.6 oxygen
Fig.6 19 minutes, 11.6 oxygen
Fig.7 21 minutes, 10.6 oxygen
Fig.8 23 minutes. 9.6 oxygen
Fig.9 25 minutes, 8.6 oxygen
Fig.10 25 minutes, 8.5 oxygen
Fig.11 After period, pure air

Plate 6. Sgt. W. D. O.

node brings about standstill of the whole of the auricular tissue. (6) The effect of the vagal stimulation in the automatic ventricle, as reported by Van Angyan, are regarded as the effects of vagal stimulation upon the A-V rhythm, for in the complete block of asphyxia the dissociated ventricle is controlled by the A-V node. (7) When at the end of simple asphyxia of the cat the auricular contractions disappear abruptly during the stage of complete A-V dissociation, the change is attributed to depression of the pacemaker, the A-V node continuing to control the movements of the ventricle."

Mathison [29] did not observe heart block on administering an excess of carbon dioxid, but when he produced asphyxia by nitrogen containing only 1 or 2 per cent. oxygen, thus preventing an excess of carbon-dioxid in the tissues, he observed heart block as "a regular occurrence during asphyxia in dogs." Block still occurred when the vagi were cut. He attributes the block to want of oxygen alone on the cardiac tissues.

Most of the investigations in this field have dealt with asphyxia produced in the usual way by cessation of respiratory movements. Both an increase of carbon dioxid and a decrease of oxygen takes place. Mathison has excluded the carbon dioxid factor in mammals. In Lewis' series of experiments the added factor of local cooling of the S-A node occurs, which adds to the complexity of experimental conditions. The rebreather method used by us eliminates the carbon dioxid by absorbing it from the exhaled air. There is, indeed, a reduction of the degree of saturation of carbon dioxid in exhaled air during the stage of augmented respiratory volume. We have recounted in careful detail the changes observed in the normal human heart that follow on simple oxygen want produced by gradual and progressive reduction of the available oxygen in the blood and body tissues to a level below which normal function can no longer occur. We reaffirm that *rhythm production in the human heart is decreased and lost at the S-A node, dissociation and block occur, and both the factor of rhythm and of conduction are lost in the descending direction during extreme oxygen want and in the absence of excess of carbon dioxid.*

These cardiac changes obviously may occur from simple oxygen want directly affecting the tissues of the heart, so that the heart can not maintain its normal function. Or the changes may be due to nerve influence as a result of asphyxial vagospasm, as shown by Mathison [29] to occur in dogs with intact vagi though he stressed the local effects. Much of our data, for example, the case of T. H. K., is not satisfactorily explained by the vagus theory, while cases like those of T. B. M. and D. W. O. look more typical of vagus inhibitions. To explain our

29. Mathison: Heart **2**:54, 1910.

terminal heart slowing and the loss of auricular beats on the hypothesis of vagus stimulation is to admit a sudden vagospasm at the close of a long period of increasing heart acceleration associated with evidence of early disappearance of normal vagal activity. Crucial tests on man are not without risk. However, we have assumed as much risk as one dares and will further discuss the significance of these changes in a paper now in preparation giving the results of a second series of electrocardiographic experiments in extreme anoxemia.[30]

## SUMMARY

1. The general changes in the type of the electrocardiogram of man with progressively induced oxygen deficiency in the air breathed are slight and compensating until a certain critical stage or crisis is reached, then fundamental intrisic changes in the cardiac mechanism begin.

2. The general and precrisis changes are: (*a*) There is a decrease or shortening of the time of the P-R interval an acceleration in conduction time, known also to be coincident with augmentation of heart rate from exercise. This augmentation is not universally observed. (*b*) There is a decrease in the total time of the R-T interval similar in type and reaction frequency to the change in conduction time but not always associated in the same test, and (*c*) there is a marked decrease in the amplitude of the T wave, with a retardation towards the terminal phase of the moment at which the maximum deflection appears. Sometimes the T wave becomes diphasic or negative at or near the crisis.

3. The precrisis electrocardiographic changes are associated with other compensating reactions to oxygen want, reactions that are expressed in the general increase in heart rate and blood pressure, and in the respiratory augmentation in minute volume of air breathed.

4. The chief postcrisis changes in the heart from extreme oxygen want are: (*a*) a great slowing of rate, (*b*), progressive descending displacement of the pacemaker or center of rhythm production toward and into the A-V node, and (*c*) interference with normal conduction leading to dissociation.

5. The postcrisis heart rate rapidly drops to a slow rhythm, in a minute or less, often in a few seconds. It decreases from 120 or 130 to 50 or 60 per minute, a drop of 50 per cent. and more. This change is associated with the development of a rhythm of auriculoventricular origin, six cases. The sino-auricular rhythm was slowed coincidently

30. Greene and Gilbert: Proc. Am. Physiol. Soc., Am. J. Physiol. **51**:181, 1920. This reference presents a preliminary report in brief abstract of the findings given in the present paper.

and disappeared altogether in extreme tests, three cases. Recovery of S-A rhythm was prompt on breathing atmospheric air.

6. In the postcrisis stage conduction was suppressed leading to complete dissociation with maintenance of auricular beats, two cases. Complete suppression of conduction occurred or was suspected in cases of absence of the *P* wave, three cases.

7. Suppression of cardiac function during oxygen want occurred in the descending direction and recovery in the reverse direction, both as regards rhythm production and conduction.

8. Experimental tests have never been carried to the point of complete suppression of the rhythm of the A-V node, or of the conducting system connecting that node with the musculature of the ventricles in man.

9. Discussion is offered comparing the hypothesis of asphyxial vagospasm and that of direct oxygen want in the tissue as mechanisms responsible for the phenomena observed in the human heart, but deciding evidence is not yet available.*

* We are under particular obligation to the commanding officers of the Medical Research Laboratory and of the U. S. General Hospital No. 9. We are also under personal obligation to Lieut. Harry Clough, who had charge of the hospital cardiographic station and under whose skill the excellent electrocardiograms were made. To the men who took the tests to the extreme limits of safety, and to the noncommissioned officers who assisted in the examinations we express appreciation and acknowledgments.

# THE DETERMINATION AND SIGNIFICANCE OF THE ELECTRICAL AXIS OF THE HUMAN HEART*

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BALTIMORE

The subject of the electrical axis of the heart has been receiving more and more attention in recent years. In the first edition of Lewis' work "The Mechanism of the Heart Beat" [1] it is not mentioned. Considerable attention, however, is given the subject in the second edition.[2] It is not too much to say that a thorough understanding of the relations of the axis is a necessary foundation of knowledge of apparently simple features of the electrocardiogram. This paper has for its purpose the presentation of a new method of evaluating the electrical axis, and a brief discussion of some aspects of the study of the subject.

## DEFINITION

By the term "electrical axis" is meant the line along which the resultant of the electrical forces acting in the heart at any instant is expressed. Or, from another point of view, it corresponds, as Lewis puts it,[2] to "the average direction in which the excitation wave is tending to move at the corresponding instant of time." This axis then is constantly shifting during the progress of the excitatory process. Therefore, one speaks of "the" electrical axis only in a more restricted sense, meaning an axis at a particular instant or a resultant axis.

## TERMINOLOGY

The electrical axis was first discussed by Waller,[3] and this worker has subsequently made many observations in this field. Waller arrived at the idea of the electrical axis by seeking an explanation of the different values of corresponding deflections of the galvanometer string obtained in various leads. His system of leads is relatively complicated and his terminology is obscure. The direction of the electrical axis is

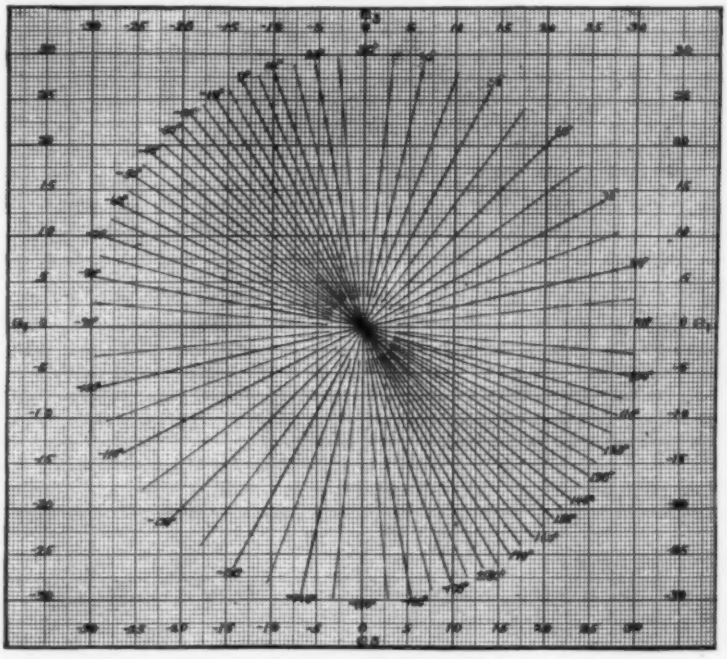
* From the Cardiographic Laboratory of the Johns Hopkins University and Hospital.
† Working under the tenure of the William Bingham Fellowship in Medicine.

1. Lewis, T.: The Mechanism of the Heart Beat, London, 1911.
2. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, London and New York, 1920.
3. Waller, A. D.: Electromotive Properties of the Human Heart, Brit. M. J. **2**:751 (Oct. 6) 1888. Electromotive Changes Connected with the Beat of the Mammalian Heart, Phil. Tr. Roy. Soc. London, B **80**:169, 1889.

expressed in terms of trigonometry. Waller worked out empirically, and later [4] proved geometrically a rather simple formula for the calculation of the angle between the electrical and the vertical axes:

$$(1)\ \text{Tan}\ a = 2\,\frac{R-L}{R+L}$$

in which "*a*" is the angle between the electrical and the vertical axis; R is the value of the deflection derived from the right arm and left foot, and L is the value of that derived from the left arm and left foot. This formula can, of course, be used for Einthoven's angle "*a*" des-



Angle "*a*" in terms of *e* I and *e* III. For description see text.

cribed below by substituting "cotangent *a*" for "tangent *a*." Waller's usage has not been followed by writers on the subject.

Our terminology is that of Einthoven.[5] Selecting from the number of leads available the three in common use, he showed that the values

4. Waller, A. D.: Various Inclinations of Electrical Axis, Pt. 1, Proc. Roy. Soc. London, B **86**:507 (July) 1913.

5. Einthoven, W.: Le Télécardiogramme, Arch. Internat. Physiol. **4**:132, 1906. Weiteres über das Elektrokardiogramm, Arch. f. d. ges. Physiol. **122**: 517 (May) 1908.

of the deflections so obtained are related as in his equation, according to which at a given instant in the cycle of the heart beat, the value of Lead II is equal to the sum of the values of Leads I and III.

$$(2)\ \text{Lead II} = \text{Lead I} + \text{Lead III}$$

He later explains this relation by comparison with the movement of a force within an equilateral triangle in which the projections of the course of the force on the sides of the triangle necessarily obey this law. The proof of this is conveniently presented in Mann's recent paper.[6] A line between the center of the triangle and any point on the course of the moving force would represent the electrical axis at that instant. The values of the deflections, and, hence, of the length of the axis are expressed in tenths of a millivolt. Einthoven refers to the length of the axis as the "manifest" value, but the term "absolute" would be clearer. The axis is defined by the angle, called "*a*," between its plane and the horizontal, which is taken as the zero line. Angles above the horizontal are referred to as negative while those below are said to be positive. This is contrary to our mathematical usage, as pointed out by Carter,[7] but it would seem best in view of the extensive work of Einthoven,[8] Lewis,[9] and Fahr [10] to continue to use this terminology.

### FINDING THE ANGLE

The fundamental equations showing the relations of the leads and the length and direction of the axis as worked out by Einthoven, Fahr and de Waart [8] are:

$$(3)\ e_1 = E \cos a$$
$$(4)\ e_2 = E \cos (a - 60°)$$
$$(5)\ e_3 = E \cos (120° - a)$$

In which $e_1$, $e_2$ and $e_3$ represent the values of the deflections in the three leads respectively; E is the manifest value or length of the axis and "*a*"

6. Mann, H.: Method of Analyzing the Electrocardiogram, Arch. Int. Med. **25**:283 (March) 1920.

7. Carter, E. P.; Richter, C. P., and Greene, C. H.: Graphic Application of the Principle of the Equilateral Triangle, etc., Johns Hopkins Hosp. Bull. **30**:162 (June) 1919.

8. Einthoven, W.; Fahr, G., and de Waart, A.: Ueber die Richtung und die manifeste Grosse, etc., Arch. f. d. ges. Physiol. **150**:275 (March) 1913.

9. Lewis, T.: Spread of the Excitatory Process, Phil. Tr. Roy. Soc. Lond. **207**: B, 221, 1916.

10. Fahr, G. E.: Analysis of Spread of Excitation Wave, Arch. Int. Med. **25**:146 (Feb.) 1920. Fahr, G., and Weber, A.: Ueber die Ortsbestimmung der Erregnung im menschlichen Herzen, Deutsch. Arch. f. klin. Med. **117**:361 (June) 1915.

the angle between the axis and the horizontal. From these data formulas were evolved the determination of "*a*" as follows:

$$(6)\ \text{Tan}\ a = \frac{2\ e_2 - e_1}{e_1\ \sqrt{3}}$$

$$(7)\ \text{Tan}\ a = \frac{2\ e_3 + e_1}{e_1\ \sqrt{3}}$$

$$(8)\ \text{Tan}\ a = \frac{e_2 + e_3}{(e_2 - e_3)\ \sqrt{3}}$$

On the basis of these formulas, Einthoven published tables by which the angle "*a*" may be determined after the values of the deflections are reduced proportionately so that the greatest is equal to 10. In a later article [11] is another table based on the same principle differently applied. One or the other of these tables, chiefly the former, has been used in the past by most of those interested in this subject.

Pardee [12] has shown that it is possible to tell by inspection of the positivity or negativity of the three leads in which quadrant the axis lies. This is because no combination of signs in the three leads occurs in more than one quadrant, which is a direct consequence of the geometric relationship pointed out by Einthoven.[5]

Fahr and Weber [10] proposed a method of direct geometric construction of the angle. The values of the deflections in two leads are measured off in any units convenient on lines inclined to one another at an angle of 60 degrees. The line representing the electrical axis runs from the vertex of the angle of 60 degrees through the junction of perpendiculars erected at the points measured off. This method is cumbersome and does not lend itself to routine use, especially in the case of angles less than 0 or greater than 90 degrees.

Recently from this laboratory Carter, Richter and Greene,[7] independently of the previous suggestion, set forth an adaptation of the same principle to the equilateral triangle. In this method a figure is used in which the geometric construction of the lead values commonly met is inserted in an equilateral triangle, about which is circumscribed a concentric circle appropriately divided into degrees. Thus the angle is found by the projection on the circle of a straight line through the center and through the point representing the lead values. This method has been in constant and extensive use in this laboratory since its inception.

In the new edition of the "Mechanism" Lewis [2] offers for use a figure showing the relative values in the three leads of a given manifest

11. Einthoven, W.; Bergansius, F. L., and Bijtel, J.: Gleichzeitige Registrirung elektrischer Ercheinungen, etc., Arch. f. d. ges. Physiol. **164**:167 (June) 1916.

12. Pardee, H. E. B.: Form of the Electrocardiogram, J. A. M. A. **62**:1311 (April 25) 1914.

value, and the changes they undergo as the axis rotates from 0 through 180 degrees to 0 again. This is not of practical value because of the difficulty, amounting almost to impossibility, of proportioning the lead values of widely varying manifest values at unknown angles.

In an interesting variation of the geometric method, Mann plots the manifest values at successive moments and connects the points by a smooth curve.[6] He uses rectangular co-ordinates of which "x" is given directly by the value of Lead I and "y" must be calculated by a formula from the values of Leads II and III. The result is a "monocardiogram" which is essentially the figure obtained by connecting the ends of the electrical axes as charted by Williams.[13] It may be plotted directly on the equilateral triangle divided as in Carter's Figure 5, without the necessity of calculating the "y" value.

It should be noted that Mann in his figures reverses the direction of the deflections in all the leads as related to the triangle, and plots positive values of "x" (= Lead I) to the left. This is at variance with the standard method of connecting the lead derivations with the string. That is, in taking the leads the lower end of the string is connected with the derivation which is normally negative, or corresponds to the zinc pole of a Daniell cell. In normal cases, therefore, the current travels down the string which is thereby deflected to the observers's right (provided the polarity of the electromagnet be properly adjusted), the movement being later described as upright. Compare Mann's Figure 2 with Lewis' Figure 13 and Williams' Figure 5.

### THE METHOD SUGGESTED

As Einthoven pointed out, there is a constant ratio between the values of the three leads with a given electrical axis.[8] It also follows from his formulas, 6, 7 and 8 above, that the angle "*a*" is determined by the ratio between the values of any two leads. This is readily apparent on inspection of the triangle as presented by Carter. But none of the methods suggested for evaluating the angle "*a*" has taken advantage of this relation, although it is, indeed, the most simple and fundamental relationship between the lead values and the angle "*a*." Table 1 gives the ratios between the values of Leads I and III at the various angles. Such a table is very much more simple to use than those of Einthoven. The ratios are derived by dividing equation (3) by equation (5), thus:

$$(9)\quad \frac{e_1}{e_3} = \frac{E \cos a}{E \cos (120 - a)}$$

$$(10)\quad \frac{\cos a}{\cos (120 - a)} = \frac{e_1}{e_3} = \text{ratio desired.}$$

13. Williams, H. B.: Cause of Phase Difference, etc., Am. J. Physiol. **35**: 292 (Oct.) 1914.

Table 1 is presented graphically in Figure 1, a chart which has been found very easy to use and which gives the result quickly. The ordinates represent values of Lead I, positive above and negative below the horizontal axis. The abscissae represent values of Lead III, positive to the right and negative to the left of the vertical axis. The values of the angles "*a*" are represented in accordance with Table 1, at the intersections of the lead values giving the proper ratios. To take an example, suppose the values + 9.5 and + 16.5 are accepted for Leads I and III of an electrocardiogram. In using the chart, one locates the point representing these values and the angle "*a*" is given by the relation of that point to the radii drawn in. In this case the point representing $e_1 = +9.5$ and $e_2 = +16.5$ is approximately at + 69 degrees. Also the ratio in this case is 0.57 + which the table of ratios shows to correspond to between + 70 degrees and + 65 degrees, much nearer the former. This figure gives the value of the angle "*a*" with all the accuracy that is desirable.

TABLE 1.—THE ANGLE "*a*" IN TERMS OF THE RATIO, $e_1/e_2$. TO FIND THE ANGLE "*a*" DIVIDE THE VALUE OF LEAD I BY THAT OF LEAD III AND UNDER THE PROPER SIGNS FOR THE LEADS SEEK THE ANGLE OPPOSITE THE RATIO SO OBTAINED

| Ratio | Angle "a" | | Ratio | Angle "a" | | Ratio | Angle "a" | |
|---|---|---|---|---|---|---|---|---|
| | $e_1+/e_2+$ | $e_1-/e_2-$ | | $e_1+/e_2-$ | $e_1-/e_2+$ | | $e_1+/e_2-$ | $e_1-/e_2+$ |
| 0.0 | +90° | − 90° | 0.0 | −90° | + 90° | −1.11 | −25° | +155° |
| +0.11 | 85 | − 95 | −0.10 | −85 | 95 | −1.23 | −20 | 160 |
| 0.23 | 80 | −100 | −0.19 | −80 | 100 | −1.37 | −15 | 165 |
| 0.37 | 75 | −105 | −0.27 | −75 | 105 | −1.58 | −10 | 170 |
| 0.53 | 70 | −110 | −0.35 | −70 | 110 | −1.74 | − 5 | 175 |
| 0.74 | 65 | −115 | −0.42 | −65 | 115 | −2.00 | 0 | ±180 |
| 1.00 | 60 | −120 | −0.50 | −60 | 120 | −2.36 | + 5 | −175 |
| 1.36 | 55 | −125 | −0.58 | −55 | 125 | −2.88 | 10 | −170 |
| 1.88 | 50 | −130 | −0.65 | −50 | 130 | −3.73 | 15 | −165 |
| 2.73 | 45 | −135 | −0.73 | −45 | 135 | −5.41 | 20 | −160 |
| 4.41 | 40 | −140 | −0.82 | −40 | 140 | −10.40 | 25 | −155 |
| 9.40 | 35 | −145 | −0.90 | −35 | 145 | − ∞ | 30 | −150 |
| ∞ | 30 | −150 | −1.00 | −30 | 150 | | | |

The manifest value which is represented by E, is determined by the value of any lead and the angle "*a*." To use the value of Lead I, for example, one takes equation (4) above:

$$(4)\quad e_1 = E \cos a$$

$$(11)\quad E = \frac{e_1}{\cos a}$$

$$(12)\quad E = e_1 \frac{1}{\cos a}$$

It follows from this last equation (12) that one can determine the manifest value by multiplying the value of Lead I as measured by the reciprocal of the cosine of the angle "*a*." Table 2 gives the values of $\frac{1}{\cos a}$ at intervals of five degrees, with interpolation values for one

degree. In the higher values the interpolations lead to slight errors, which are inevitable. (For the angle "a" $= +90$ degrees we cannot use Lead I as the factor $\frac{1}{\cos a}$ is infinity; hence Lead III is substituted.) Suppose, for example, Lead $1 = 5$ and "$a$" $+65$ degrees. Then $\frac{1}{\cos a} = 2.37$, which multiplied by 5 gives 11.85, the value of E.

TABLE 2.—THE VALUE OF $\frac{1}{\cos a}$. THE MANIFEST VALUE IS OBTAINED BY MULTIPLYING THE VALUE OF LEAD I BY THIS FACTOR

| Angle "a" | | $\frac{1}{\cos a}$ | Interpolation for 1° | Angle "a" | | $\frac{1}{\cos a}$ | Interpolation for 1° |
|---|---|---|---|---|---|---|---|
| ±0° | ±180° | 1.000 | 0.001 | ±50° | ±130° | 1.56 | 0.035 |
| 5° | 175° | 1.004 | 0.002 | 55° | 125° | 1.74 | 0.05 |
| 10° | 170° | 1.015 | 0.004 | 60° | 120° | 2.00 | 0.07 |
| 15° | 165° | 1.035 | 0.006 | 65° | 115° | 2.37 | 0.11 |
| 20° | 160° | 1.064 | 0.008 | 70° | 110° | 2.9 | 0.2 |
| 25° | 155° | 1.104 | 0.01 | 75° | 105° | 3.9 | 0.4 |
| 30° | 150° | 1.155 | 0.013 | 80° | 100° | 5.8 | 0.9 |
| 35° | 145° | 1.221 | 0.017 | 85° | 95° | 11.5 | |
| 40° | 140° | 1.305 | 0.022 | 90°* | .... | 1.155° | 0.013° |
| 45° | 135° | 1.41 | 0.03 | | | | |

* For "a" = 90° use lead III.

It should be emphasized that all these "methods" have the same underlying principle and with the exception of that of Waller as explained above, are designed to reach the same result.

In practice two difficulties arise in connection with the determination of the angle "*a*." First, since the electrical axis is constantly shifting throughout the cycle of the heart beat, what axis or axes shall be determined? For certain purposes it is helpful and of great interest to determine the direction of the axis at short intervals throughout the cycle or a part of it. Tabulation of the results, showing clearly the mode of shifting present, is very instructive.[14] But for practical reasons this is only possible in a limited number of cases. In general, the axis is determined only for that time instant when the greatest potential difference is recorded by one or more of the leads, i. e., at the peak of the Q R S complex. This is then spoken of as "the" electrical axis; but in many ways this is misleading. It is not unlikely that as the subject is developed it will appear that the axis should be determined at different instants for different purposes.

Secondly, what parts of the curves in the two or three leads shall we measure? The law of the relationship of the leads is only true of corresponding time instants in the leads. It has been shown that the peaks are often not in phase. Strictly, then, simultaneous leads or leads taken with simultaneous phonocardiograms should be used.[15] Unfor-

14. Grau, H.: Ueber der Einfluss der Herzlage auf die Form des Elektrokardiogramms, Ztschr. f. klin. Med. **69**:281, 1910.

15. Fahr, G.: Simultaneous Records of Heart Sounds and the Electrocardiogram, Heart **4**:147 (Nov.) 1912.

tunately neither of these methods is available for extensive application. Lewis [9] adjusts enlarged graphs of the three leads, one above the other, until the measured values in all leads at a number of instants are all within the law that Lead II is the sum of Leads I and III. This is the most satisfactory method which is at present available. For the routine determination of the electrical axis in a large number of cases we can only use the values of the peaks of the Q R S group. In general this gives a value which is not widely at variance with the accurate value of the angle "*a*" for the time chosen.

### THE NORMAL ELECTRICAL AXIS

It has been found that the vast majority of normal electrocardiograms show electrical axes at the instant of greatest potential difference that lie within a restricted portion of the compass. Different observers have placed varying limits upon the normal variation but the precise limits are not matters of great importance. Einthoven, Fahr and de Waart [8] placed the normal limits at 40 and 90 degrees, Waller [16] at — 10 degrees and 100 degrees. Carter and Greene [17] adopted 0 degrees and 90 degrees which may be followed provided too much emphasis be not placed on slight variations beyond these limits. This limitation certainly embraces nearly all normal cases.

Certain important practical points are explained by consideration of the electrical axis and the manifest value. A few of these may be briefly outlined.

### THE EFFECT OF RESPIRATION

The angle "*a*," as is now well-known, changes with respiration, being greater in inspiration and less in expiration.[18] In more general terms, the same changes occur respectively with descent and ascent of the diaphragm, whatever the cause (compare, for example, the effect of gastric distention). The change in direction of the axis is from 5 to 35 degrees in extent. The form of the electrocardiogram as a rule, is not altered by this change, though the height of the chief ventricular waves in Leads I and III always varies somewhat with the respiratory phase. Lead II shows the variation more rarely and to a less degree for the reason that most axes are more nearly parallel to the plane of that lead and variations in the angle under that condition have less effect upon the value of the lead. This can be seen expressed mathematically for Lead I in Table 2.

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16. Waller, A. D.: Various Inclinations of Electrical Axis, Pt. 1A, Proc. Roy. Soc. Lond., B **88**:49 (Aug.) 1914.

17. Carter, E. P., and Greene, C. H.: Electrocardiogram and Ventricular Preponderance, Arch. Int. Med. **24**:638 (Dec.) 1919.

18. Waller, A. D.: Effect of Respiration on Electrical Axis, J. Physiol. (Proc.) **46**:57 (Aug.) 1913.

It has, however, often been observed [19] that certain electrocardiograms show a change of R to S in Lead III and certain others a change of S to R in the same lead. It is Lead III which shows this change because the various axes are usually more nearly at right angles to the plane of this lead and therefore slight changes of direction have marked effects upon the value of the lead. A glance at Figure 1 shows the geometric explanation of the change in direction of the waves. At the angle 30 degrees Lead III is equal to 0, or, in other words, the current direction is at right angles to the lead plane and no movement of the string is recorded. At angles below 30 degrees Lead III has a negative value and above 30 degrees a positive value. Hence, in a heart whose axis is close to 30 degrees the value of Lead III may be changed from positive to negative by a good expiration; or, vice versa, by a deep inspiration depending on which side of 30 degrees the axis starts from. It should be noted that in most cases these changes are produced only by respiratory movements of more than normal excursion.

The peculiarity of Lead III just discussed underlies the widespread feeling that alterations in this lead should not be emphasized. But it would be better to bear this explanation in mind and use Lead III for whatever information it may contribute. Interestingly enough it will be seen that in cases of "situs inversus" Lead II becomes the unstable lead and Lead III relatively stable.

In measuring curves which show a marked respiratory variation in excursion the high R values in Lead I should be taken in conjunction with low R values or with high S values in Lead III. This follows from the direction in which the axis shifts as explained above.

### THE EFFECTS OF THE POSITION OF THE BODY

Moderate changes in the position of the body have but little effect on the electrical axis. The angle *"a"* is from 10 to 15 degrees greater in the standing than in the sitting or in the prone position. It is usually about the same when the patient is lying on his back as it is when he is seated. In the left lateral decubitus the angle *"a"* is increased by about 15 degrees, and decreased somewhat less in the right lateral decubitus.[19]

### EFFECT OF OTHER DISPLACEMENTS OF THE HEART

One of the earliest observations [3] in this field was of the effect of "situs inversus." Here the effect is complete and the explanation obvious.

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19. Waller, A. D.: Voluntary Reversal of Human Electrocardiogram by Deep Respiration, J. Physiol. (Proc.) **48**:40 (July) 1914.

Alterations in the position of the heart produced in other ways, in general, do not have marked effects. Pneumothorax, pleural effusion and similar conditions cause but slight shifting of the electrical axis.

### VENTRICULAR PREPONDERANCE

In the minds of many the subject of the electrical axis is linked inseparably with that of ventricular predominance because it is in this connection that the axis finds its most obvious clinical application. It was first pointed out by Einthoven [5] that "hypertrophy" of one or the other ventricle is associated with characteristeric electrocardiographic findings, now too well known to need repetition. These peculiarities were definitely related to the anatomical conditions by two series of hearts examined by Lewis [20] and Cotton.[21] At the same time, Lewis suggested that in this connection the term "preponderance" rather than "hypertrophy" should be used. It should be recalled that there is normally a left ventricular preponderance present. The normal weight ratio, L/R, probably ranges between 1.6 and 2.1. When the expression left preponderance is used, then, it means that the left ventricle is thought of as weighing more than 2.1 times as much as the right ventricle.

The features of the electrocardiogram under discussion are such that they can only be interpreted as reflections of peculiarities of the electrical axis. The "high R" in Lead I and "deep S" in Lead III signify a negative angle *"a"* (S in Lead III first appears at an angle of 30 degrees). The "S" in Lead I and "high R" in Lead III are projections of an axis at an angle greater than 90 degrees (S in Lead I first appears at that angle). Lewis and his co-workers [9] have shown that the underlying change in the axis concerns the direction in which it rotates. Normally, the electrical axis rotates uninterruptedly in a clockwise direction. In case of right ventricular preponderance the rotation is in the same direction but very quickly reaches high values for *"a"* and extends farther. When the left side is preponderant, the direction of rotation is counter-clockwise and the extreme deflections are at negative angles. These departures from the normal are due to a disturbance in the relation between the dextrocardiogram and levocardiogram of which the ordinary electrocardiogram is a summation.

So much it would seem is beyond controversy. Lewis [2] says there is little reason to doubt that Einthoven's conclusions are valid, and strongly suggests that it should not be assumed in case of incompatibility between clinical and electrocardiographic evidence that the latter

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20. Lewis, T.: Observations on Ventricular Preponderance, etc., Heart **5**: 367 (July) 1914.

21. Cotton, T.: Observations on Hypertrophy, Heart **6**:217 (Oct.) 1917.

is necessarily at fault. The suggestion that dilatation rather than mass preponderance may sometimes be present has been made by Waller [22] and by Fahr,[23] a suggestion which in the light of our present knowledge needs supporting evidence. In a recent paper Fahr [24] has advanced the theory that the abnormalities of the electrocardiogram under discussion are due to changes in the relations between the lengths of the bundle branches on the two sides. This theory is at present without a satisfactory experimental basis.

In using the electrical axis for the purpose of estimating ventricular preponderance fixed limits of normality are necessary, and 0 to 90 degrees may be used, provided one bears in mind three points. First, that the normal respiratory variation may be as much as 30 degrees. Secondly, that it is not intended to attach much significance to angles just beyond the limits of normality. And thirdly that there are other causes of abnormal angles, such as "situs inversus" and bundle branch blocks. With regard to the limits defined above, it is easy to remember that the angle "*a*" is negative when the value of Lead III is negative and the ratio between the value of Lead I and that of Lead III is less than 2 (a negative value in Lead III does not necessarily mean a negative angle). A negative value in Lead I in conjunction with a positive value in Lead III, however, always means an axis at an angle greater than + 90 degrees.

Carter and Greene,[16] in a paper from this laboratory, endeavored to show the general correspondence between the angles of the greatest potential difference developed and the ratios between the weights of the ventricles in the few cases (fifteen in all) in which the necessary data exist. These data are those of Lewis [20] and Cotton.[21] It was pointed out that the agreement is, in fact, striking, with the exception of three cases. Explanation of two of these cases was offered by Cotton on the ground that considerable time had elapsed between the taking of the electrocardiogram and the postmortem examination.[25] It was proposed by Carter and Greene to determine the direction of the electrical axis for this purpose by using the values obtained by the algebraic subtraction of the value of S from that of R in Leads I and III on the ground that these waves represent the opposite effects of the two ventricles in the rotation of the axis. The angle "*a*" thus obtained is to be regarded as a resultant.

22. Waller, A. D.: Electrical Axis of the Human Heart, Lancet **1**:1435 (May 24); 1513 (May 31) 1913.

23. Fahr, G.: Clinical Application of Electrocardiography, J. Mich. M. S. **17**:10 (Jan.) 1918.

24. Fahr, G. E.: Principles of Electrocardiography, Arch. Int. Med. **27**: 126 (Jan.) 1921.

25. Stewart, H. A.: Experimental Contribution to Study of Cardiac Hypertrophy, J. Exper. M. **13**:187 (Feb.) 1911.

This attempt at a quantitive estimation of the electrocardiographic evidence was criticized by Pardee,[26] who concluded that either of two empirical formulas gave the results nearer to the weight ratios. The first of these formulas was used by Lewis in arranging his electrocardiographic findings in the cases in which he had obtained the ventricular weight ratios, at a time when attention had only recently been drawn to the electrical axis. The second is that offered by White and Block.[27] These formulas are essentially similar. Pardee's conclusions were based on the ground that the Lewis and White formulas misplace fewer cases in the weight ratio series. The results are shown graphically in a chart (Fig. 1). This figure is misleading, however, because the weight ratios are represented on one scale, the figures obtained by the formulas on another and the angle *"a"* on a third scale, so that the results are not comparable.

Examination of Lewis' formula shows that it cannot under all circumstances give a figure representing the electrocardiographic findings. The formula is:

$$(13)\ R_1 - R_3 + S_3 - S_1 = \text{index}.$$

This index is 0 when the angle *"a"* as determined by Carter and Greene is 60 degrees and also when it is — 120 degrees. For instance, suppose $R_1 = 12$, $S_1 = 5$, $R_3 = 10$, $S_3 = 3$ (*"a"* = 60 degrees); and in a second case $R_1 = 4$, $S_1 = 10$, $R_3 = 2$, $S_3 = 8$ (*"a"* = —120 degrees). In both cases the index is 0. However one determines the angle *"a,"* it is evident that Lewis' figure fails to show the complete reversal of the electrocardiographic data. In general, Lewis' formula gives a high positive figure with left ventricular preponderance and a negative figure with preponderance of the right chamber. A further example of the possible discrepancies may be given from our records:

| Case No. | $R_1$ | $S_1$ | $R_3$ | $S_3$ | Lewis' Index | *"a"* |
|---|---|---|---|---|---|---|
| 2314 | 12.0 | 0. | 4.0 | 1.5 | 9.5 | + 39° |
| 2237 | 7.0 | 3.0 | 1.5 | 6.5 | 9.0 | — 40° |

Here, again, the electrocardiographic evidence is certainly not expressed by Lewis' index.

The occurrence of waves of large amplitude in cases of left or right ventricular preponderance is pointed out by Pardee. In the case of left-sided preponderance, the largest waves are all $R_1$ or $S_3$, while for preponderance of the right ventricle these are $S_1$ or $R_3$, facts to be expected on the ground of Lewis' explanation of the electrocardiogram as a summation of separate, largely opposing elements due to the spread of the excitation wave through the left and right ventricle

26. Pardee, H. E. B.: Determination of Ventricular Preponderance, Arch. Int. Med. **25**:683 (June) 1920.

27. White, P. D., and Bock, A. V.: Electrocardiographic Evidence of Abnormal Ventricular Preponderance and of Auricular Hypertrophy, Am. J. M. Sc. **156**:17 (July) 1918.

respectively.[9] It seems impossible that consideration of the deflection in one lead alone can be of value, since, for instance, a high $R_1$ of given value, has an entirely different significance in conjunction with a negative value in Lead III from that which it has with a positive value in Lead III.

In view of the basis described for the use of the electrical axis in estimating ventricular preponderance, it does not seem that the method should be discarded because of the discrepancies in the series of fifteen cases referred to above.

## AURICULAR HYPERTROPHY

There is suggestive evidence that hypertrophy of the auricles is sometimes associated with "P" waves of increased amplitude.[27] In estimating the height of the "P" wave the manifest value should be used because of the influence of the direction of the axis on the length of the lead values. In connection with the value of "P" in Lead I, Table 2 can be used for this purpose.

Space does not permit the analysis, but it can readily be appreciated that an understanding of the principles of the electrical axis is essential to the intelligent interpretation of split and bizarre complexes, and of the curves of premature systoles and bundle branch blocks.

## SUMMARY

1. The definition of the electrical axis is repeated and the various methods proposed for evaluating the angle "*a*" are outlined.

2. That the angle "*a*" depends upon the ratio between any two leads is demonstrated and tables for the direct determination of the angle "*a*" and the manifest value, with a graph for finding the angle by inspection are given.

3. As evidence of the fundamental importance of the electrical axis its relations to the effects of respiration, the position of the body and other causes of displacement of the heart, on the electrocardiogram are pointed out.

4. The use of the angle of the electrical axis at the instant of greatest potential difference in estimating ventricular preponderance is discussed. As far as our knowledge at present goes, this angle probably gives the most accurate indication of the condition present.

Acknowledgment is made of the kind supervision of this paper by Dr. E. P. Carter.

# PAROXYSMAL TACHYCARDIA

## WITH REFERENCE TO NOMOTOPIC TACHYCARDIA AND THE RÔLE OF THE EXTRINSIC CARDIAC NERVES *

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Of the recognized disorders of the cardiac mechanism, none possess greater interest than the paroxysmal tachycardias. This affection has been recognized as a clinical entity for more than thirty years, and the condition has been produced experimentally by various means. Two questions have recently been revived; one, concerning sites of origin, especially the possibility of a paroxysm arising at the sino-atrial node (nomotopic tachycardia) and the other, concerning the rôle of the extrinsic nerves of the heart. Herewith I wish to report six cases [1] of paroxysmal tachycardia which illustrate the moot points and the variety of clinical conditions in which the disorder occurs.

### REPORT OF CASES

CASE 1.—J. W., aged 19 years, student. This patient was first seen Dec. 30, 1919, when he came for examination because of unduly rapid and forceful heart action which frequently occurred following exercise. He says they have been present as long as he can remember, and his mother recalls attacks as early as 5 years when the child often ran to her, frightened because of the abnormal cardiac activity. An aunt has told him that when he was a small boy she had noticed that his heart was extremely rapid when at play. Rarely, pounding of the heart is experienced at night but usually there is no consciousness of the heart except during the attacks. The paroxysms are often related to exercise but from consideration of many attacks it is clear that they are not dependent on the total energy expended but rather follow sudden or spasmodic effort. Attacks have occurred irregularly during gymnasium exercises, following certain maneuvers in military drill, swimming, especially just after plunging into cold water, after a sudden spurt for a car or coughing. But in carefully planned gymnasium work and hard labor in the hay field during the summer the pulse rate does not rise above 80. At the laboratory attacks have followed running up and down stairs but at other times this exercise or hopping until dyspnea necessitated rest did not bring on a paroxysm. The emotional factor is seen in the occurrence of paroxysms while dancing and while watching an exciting football match. These attacks always begin suddenly and cease abruptly; according to the patient, "it is just like shifting gears on a car." The duration is from a few minutes to two hours. He thinks he often stops an attack by holding his breath or throwing himself suddenly across a bed or convenient object, and says that recently an attack ceased promptly after pressure on the right eyeball. During the attack the heart beats rapidly and

* From the Electrocardiographic Laboratory of Mercy Hospital.

1. These patients were referred by Drs. J. A. Lichty (Cases 1, 4 and 5), E. M. Frost (Case 2), J. I. Johnston (Case 3), and G. L. Hays (Case 6), to whom I express my indebtedness.

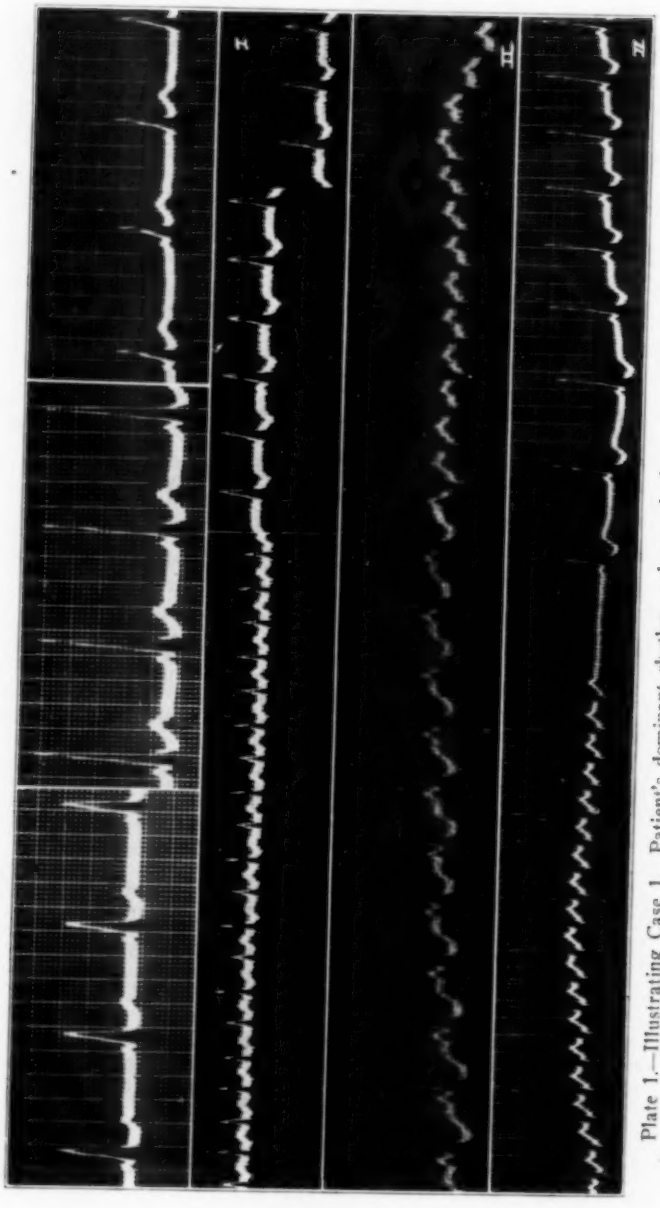


Plate 1.—Illustrating Case 1. Patient's dominant rhythm and records from paroxysm of Dec. 31, 1919. In Lead II the arrow marks the application of pressure on the right vagus.

forcefully; breathing is labored; the skin becomes flushed; he feels very warm, and perspires profusely. Occasionally, there has been pain about the heart.

*Examination.*—April 4, 1920, the patient visited the laboratory. The pulse rate varied from 72 to 80, with sinus arrhythmia; blood pressure, 104/58; skin dry; pupils moderately dilated. After running eight times up and down a flight of twenty-four steps he returned to the laboratory saying "I am winded and it has not started yet." As he sat down the paroxysm began suddenly. Then the following observations were made:

PULSE RATE AND BLOOD PRESSURE OF J. W. (CASE 1) DURING A PAROXYSM

| Time | Pulse Rate | Blood Pressure |
|---|---|---|
| 11:45 | 74 | 104-58 (Before exercise) |
| 12:07 | 184 | 144-80 (After exercise) |
| 12:10 | 180 | 130-74 |
| 12:12 | 180 | (Breath held) |
| 12:14 | 116 | 115-76 |
| 12:19 | 104 | 105-75 |
| 12:40 | 106 | 103-65 |

The pupils did not show any appreciable change; with the onset of the paroxysm the face became markedly flushed and a drenching sweat supervened. This attack was typical; variation is solely in duration.

*Family History.*—The family history is interesting. The paternal grandfather died suddenly at 48; he is said to have had a "tobacco heart." Three of the four sisters of the father have suffered from toxic goiter. A sister died of tuberculosis.

*Previous History.*—The patient himself has had measles, mumps, chickenpox and whooping cough when a small boy; diphtheria at 9 years and pneumonia at 13. There is no history of rheumatism or tonsillitis. Growth has been normal and general health has been excellent. There are no abnormal symptoms and the young man leads the life of an active college student, though handicapped by the irregular occurrence of the paroxysms.

*Physical Examination.*—The essential points in the physical examination were: Development and nutrition, good. No gross abnormalities.

Skin: Dry. Normal distribution of hair. Dermographia, central red line with a broader zone of blanching on either side.

Eyes: Pupils variable, often quite widely dilated.

Mouth and Throat: Negative.

Neck: No enlargement of thyroid.

Lungs: Negative.

Heart: Localized apex impulse in fifth interspace. Precordial dulness not increased. Sounds are of good quality and unaccompanied by murmurs. A 2 accentuated. Sinus arrhythmia with rate varying between 60 and 90. Blood pressure: systolic, 100-126; diastolic, 58-76.

Abdomen: Negative.

Reflexes. Normal.

*Fluoroscopic Examination.*—No enlargement of heart. Quick, forceful pulsation, with rather jerky retraction of apex and unusually forceful pulsation of the aorta. Lungs were clear.

Roentgenogram of skull showed no abnormality of sella turcica. Blood cytology: normal. Wassermann reaction, negative. Basal metabolism: normal.

*Reaction to Drugs.*—Atropin, 0.03 gm., rate increased from 60 to 100. The arrhythmia disappeared. In the electrocardiogram the P-R interval remained unchanged; T waves became inverted, returning to upright form in one hour. Pilocarpin, 0.12 gm.: no general reaction. No variations in details not seen normally. Epinephrin, 1 mg. No effect that could be attributed to it.

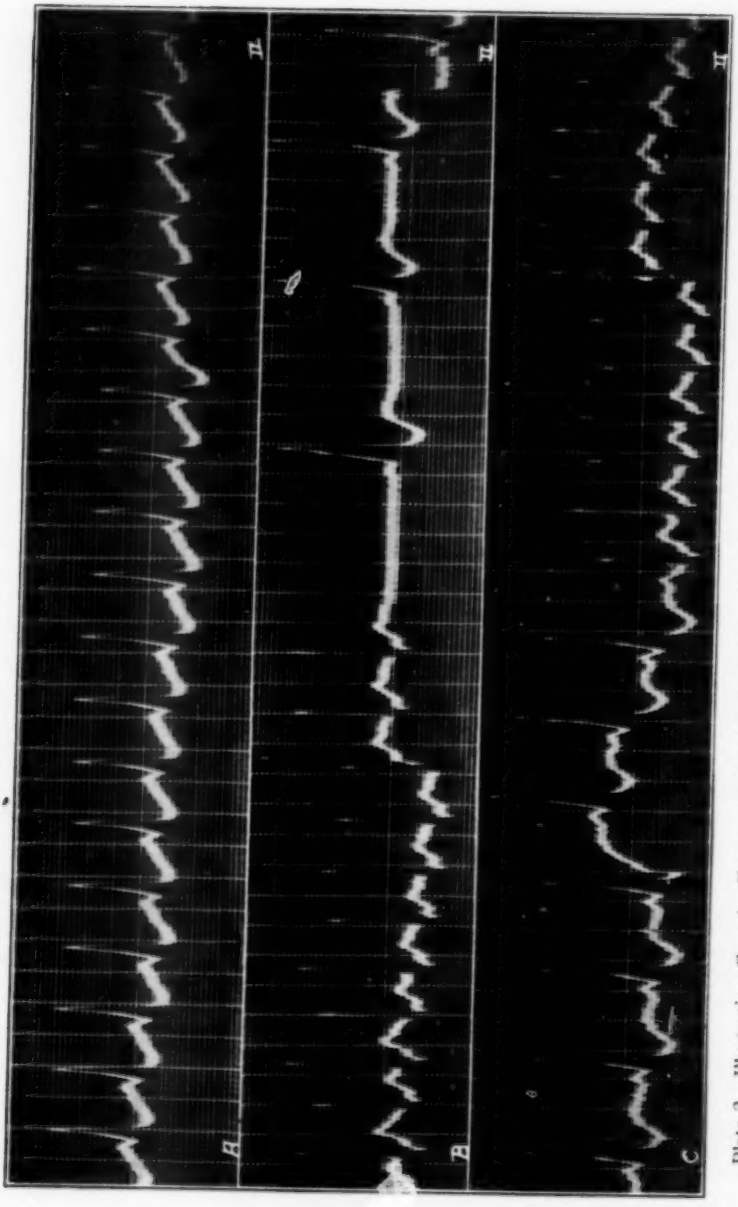


Plate 2.—Illustrating Case 1. From records taken Dec. 17, 1920. A. After exercise, rate 150. B and C are continuous.

*Electrocardiograms.*—The dominant rhythm has always been an A-V arrhythmia; P-R interval, 0.08 second; width of R, 0.12 second; T waves upright. Following exercise, atropin and the paroxysms, the T waves were inverted. The first beat of the paroxysm begins at the end of the normal interval of the fundamental rhythm, with an instantaneous doubling of the P-R interval, halving of the duration of R, and inversion or disappearance of T. The termination of the new rhythm is apparently by the production of a vagus block, prolongation of conduction time and failure of ventricular response. The rate of the paroxysm is from 180 to 195; variation in the R-R intervals occurs and at times is due to variation, amounting almost to alternation, in the P-R interval. The figures in Plate 1 were taken in the latter part of December, 1919. Plate 2 was recorded Dec. 17, 1920.

Case 2.—A woman, 52 years of age, had suffered for many years from hyperacidity and constipation, associated with alimentary stasis which is the result of marked visceroptosis. The examination of the cardiovascular system is negative, except for the disturbance of the cardiac mechanism. Ectopic beats are known to have been present for the past five years. The first attack of paroxysmal tachycardia occurred in February, 1919. Since then paroxysms have been of frequent occurrence; they often come on in the early morning hours or after meals and have varied in duration from a few minutes to eight hours. Vagus pressure has been tried by several physicians, none of whom have succeeded in stopping the paroxysm by that means. Relief has usually followed emptying the stomach by an emetic. The ectopic beats are seen to arise in the left ventricle. However, the electrocardiogram taken during the paroxysm indicates that the new rhythm arises in the A-V node and that reversal of the mechanism occurs; the type of curve suggests some defect in conductivity of the left branch of the bundle (Plate 3). The illustration was recorded during the afternoon of Oct. 27, 1919. The paroxysm began about 1 p. m. Vagus pressure, aromatic spirits of ammonia, atropin 0.025 gm., and, finally, the passage of a stomach tube failed to arrest the paroxysm, which continued with occasional interruptions by a few normal beats until about 8 p. m. when it suddenly stopped. There was no cyanosis or dyspnea during the attack. The atropin caused marked dryness of the mouth and blurring of vision. Of late there have been no attacks. This is attributed to daily gastric lavage.

Case 3.—This patient, a single man, aged 24 years, was referred April 6, 1920, with the complaint that on going to bed at night his heart became irregular and rapid, there being a succession of attacks during which the heart suddenly "started up," beat rapidly for a few minutes and then stopped abruptly. There was no pain, no shortness of breath and no symptoms other than the consciousness of the irregularity and this prevented sleep. The condition had been present since his discharge from the army in May, 1919, and was attributed to confinement in an office. He had influenza in January, 1919, while in France.

There has been no loss of weight or strength nor unusual fatigue. He plays volley ball and bowls regularly, without any symptoms referable to the cardiovascular or respiratory system. The hands and feet were often unduly moist, though the skin activity, in general, was not excessive; lacrimation or salivation has not occurred.

The family and the patient's past history are without significance. He has not had either rheumatic fever or tonsillitis. Venereal diseases were denied; the blood Wassermann reaction was negative.

*Physical Examination.*—Development and nutrition, good.

Skin: Generally dry, except the palms which were cold and clammy. Red line dermographia.

Eyes: Palpebral fissures abnormally wide; pupils dilated. Muscular reactions normal.

Mouth: Teeth good; no apparent pathology in tonsils.

Neck: No enlargement of thyroid.

Lungs: Negative.

Heart: Apex beat in fifth interspace. No enlargement of percussion dulness. Sounds of good quality, without murmurs or abnormal accentuations. Rhythm, irregular due to the occurrence of frequent ectopic beats and short paroxysms of tachycardia. The systolic blood pressure varied between 90 and 112 and the diastolic from 60 to 75; during the paroxysms the systolic pressure fell to 80; the diastolic could not be read.

Abdomen: Negative.

Reflexes: Those at elbows and the knee jerks were exaggerated; plantar response, normal.

Blood: Cytology, normal except for a slight leukocytosis, 9,400 present during the second examination which was probably due to recent pharyngitis.

Paroxysms of tachycardia were of frequent occurrence. The taking of the pulse by the nurse or any of the laboratory procedures were sufficient to cause their appearance. They were usually of very short duration, lasting from a few seconds to one half hour, and averaged about 100 cycles. The average rate during the spontaneous paroxysm was 162, with variation of about 0.02 second in the R-R interval. The normal electrocardiogram is that characteristic of excessive sympathetic tone, with relatively large P and T waves and low R. Periods of slow nodal rhythm were seen occasionally. The paroxysms are believed to arise in the A-V node. In Lead I is seen a nodal beat, followed by a beat with a short P-R interval, then P is definitely behind R when the paroxysm begins. At the end of the paroxysm was either a negative P wave or the last beat showed a small upright T and resembled many of the isolated nodal beats (Plate 4).

Epinephrin was without any effect, and while pilocarpin produced intense sweating there did not seem to be any specific effect on the electrocardiogram. However, following the injection of 0.03 gm. atropin a paroxysm came on in a few minutes which continued at a rate of 184 during one and one-half hours that the patient remained in the laboratory, and according to him did not stop for four hours.

Case 4.—A farmer, aged 63, came to the hospital for prostatectomy. When first seen there was an irregularity due to occasional ectopic beats which arose at a low level in the atrium. A similar irregularity of the pulse was noted eight years ago when he had an eye infection. There has been no dyspnea on exertion, no thoracic pain, no edema of the extremities.

*Physical Examination.*—The prominent points of the physical examination were: The face was flushed and there was slight cyanosis of the lips. The lungs showed marked senile emphysema. The heart was not enlarged: there were systolic murmurs at both the apex and over the aortic area: the aortic second sound was accentuated. Blood pressure, 130/80. The first paroxysm was recorded Dec. 3, 1919. When questioned the patient said he had noticed slight discomfort about the heart but thought nothing of it. Subsequently many attacks were observed; it was not unusual for one to begin during a bedside examination. One attack is known to have lasted two hours. The patient was never conscious of the abnormal rhythm and the surgical history was uneventful.

From a comparison of electrocardiograms showing the isolated premature beats and those of the paroxysms, it seemed that the two arose at the same focus. The paroxysm is typical of the atrial tachycardias which arise well below the pacemaker. The illustration was obtained Jan. 24, 1920 (Plate 5, A). Pressure on the right vagus was exerted fourteen cycles before the effect noted. Although the paroxysm soon returned, this is doubtless an example of an ectopic rhythm which was influenced by vagus pressure.

Case 5.—Man, aged 77 years, whose sole complaint was that he had had a bad taste in his mouth for the past five years. He has been short of breath on exertion for many years, but has never had any edema nor has he been conscious of any abnormal cardiac activity.

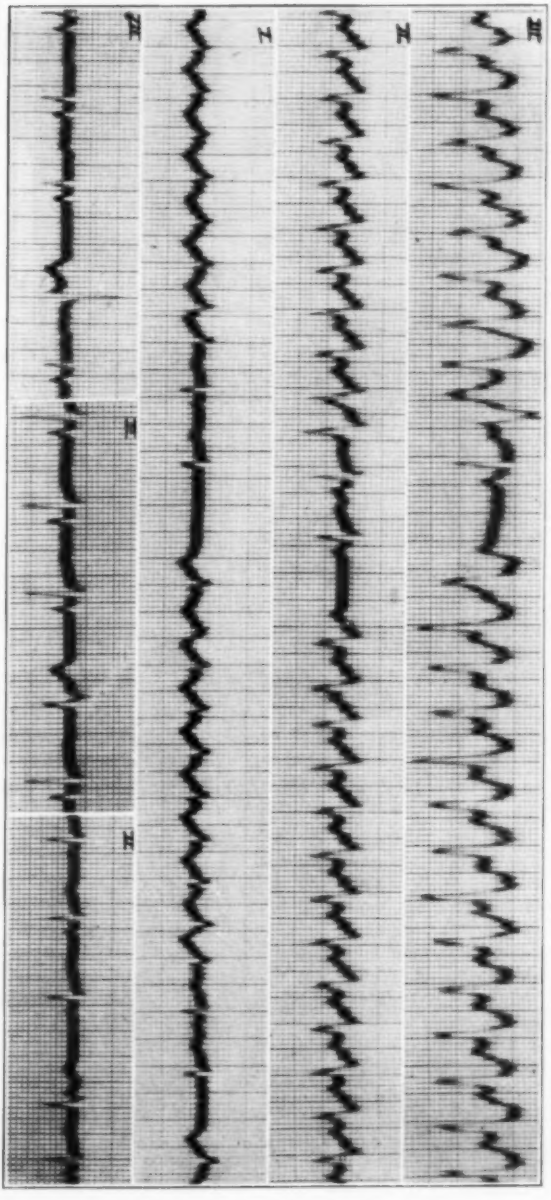

Plate 3.—Illustrating Case 2. Normal mechanism (Lead II on different days) and paroxysm.

*Physical Examination.*—Skin: Deep cyanosis of lips, tongue and oral mucosa.

Lungs: Senile emphysema.

Heart: Slightly enlarged to the left. Systolic murmur heard over entire precordium and transmitted to vessels of the neck. Rhythm, very irregular. Blood pressure, 200/80. Marked thickening of the peripheral vessels.

Abdomen: Liver enlarged and tender to pressure.

Extremities: Negative.

*Fluoroscopic Examination.*—Slight enlargement of heart. Localized enlargement of the arch of the aorta, an exaggeration of the usual senile knuckling. Marked opacity of the aorta.

*Electrocardiogram.*—Shows numerous ectopic beats which arise at two different levels in the atrium and in the left ventricle; also short paroxysms of tachycardia originating at a low level in the atrium. The last two cycles of the paroxysm suggest a shifting of the pacemaker to a higher level in the atrium (Plate 5, B). Because of the short duration of the paroxysms it was not possible to judge the effect of vagus pressure.

CASE 6.—The patient, a woman, aged 58 years, was in the hospital during the week of Jan. 3, 1921, suffering from pain in the lower right quadrant of the abdomen. A mass is said to have been palpated and an exploratory laparatomy advised, but the patient refused operation and left the hospital on the afternoon of January 10. The next morning, about 4 o'clock, she was heard moaning by her niece with whom she was staying. She seemed very weak, was unable to speak for several hours, the pulse was almost imperceptible and the family believed she had suffered a stroke. A physician was called later. He noted the rapid heart action. The following day, January 12, the patient was brought back to the hospital.

*Physical Examination.*—Examination was made at 7 p. m., the principal details of which were: A well developed and well nourished woman, whose appearance when first seen suggested that she was ten years older. She was able to recline without pillows, and was free from pain or any discomfort, except the consciousness of a rapid and pounding heart. The lips and fingers were slightly cyanotic. The lungs were negative; no moisture was present. In the abdomen, the liver edge was palpable, and there was tenderness on pressure over the cecum. The heart was enlarged a little to the left. Both sounds were very weak, unaccompanied by murmurs and without accentuations. The apex rate was 180, and the rhythm was regular, and although the radial pulse was very weak, all beats came through to the wrist. Blood pressure, 95/82. The electrocardiogram showed a regular tachycardia with a rate of 180. The type of curve was supraventricular and from careful examination of a considerable length of record it is believed to have had its origin in the lower part of the A-V node, and that reversal of the mechanism occurred, the P wave appearing as a small notch at the end of R (Plate 5, C). Holding the breath, pressure on the vagus in the neck and on both eyeballs was without any influence whatsoever on the rhythm.

*Clinical Course.*—Morphin was given and the patient rested well throughout the night. At noon, January 13, the apex rate was still 180; blood pressure, 95/75. Crepitant räles were heard at both bases, and the liver seemed larger than on the first examination. There was no dyspnea and she was comfortable except for the palpitation. Tincture of digitalis in 5 c.c. doses was given at 2 and at 4 p. m. Promptly, after the second dose, according to the patient, she vomited a large amount of "bile," the heart suddenly became slower and she dropped off to sleep. When seen at 7 p. m. the improvement in general appearance was quite srtiking. The pulse rate was 84 and the blood pressure 122/85. The electrocardiogram showed a normal mechanism.

January 15 a short paroxysm was reported but not studied. Examination the following day showed the pulse rate to be 80 and the blood pressure 145/75; the lungs were free from moisture and the liver was not palpable.

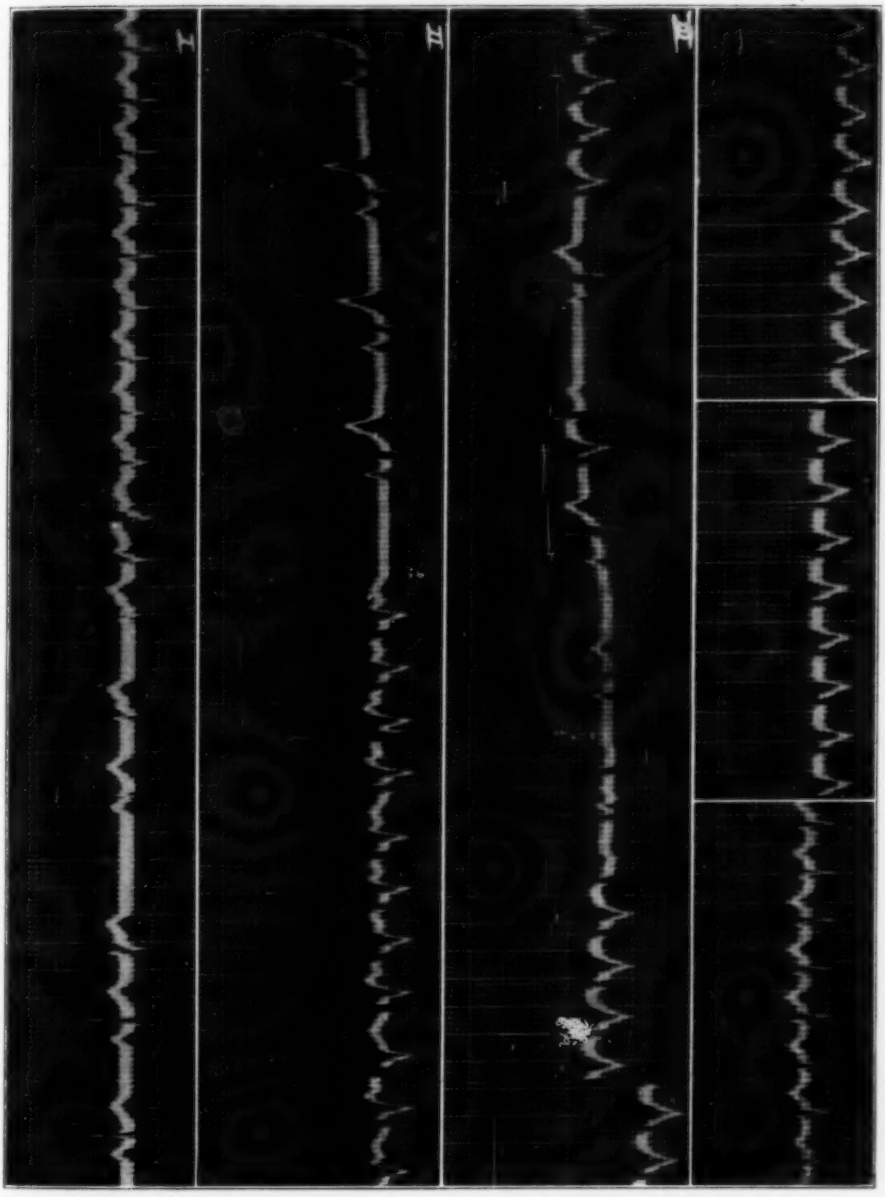


Plate 4.—Illustrating Case 3. Spontaneous paroxysms and paroxysm one hour after 0.02 gm. atropin (fourth line).

Subsequent questioning brought information to the effect that since she was 15 years old the patient had suffered from such attacks which were characterized by very rapid beating of the heart. They frequently came on when at school; at times they were related to fatigue and again occurred during the night. No definite precipitating causes have been known. Fainting often occurred at the onset. Almost invariably the paroxysm has stopped after vomiting. Frequent examinations by numerous physicians have failed to reveal any signs of heart disease and physical and radiographic examinations during the week following the long paroxysm showed no evidence of disease either of the valves or of the myocardium. The previous paroxysm occurred last October. The one described was of the longest duration, having lasted for at least sixty hours.

This case is especially interesting in comparison with the first case cited, and recalls the analogy of Bouveret between epilepsy and paroxysmal tachycardia in that the individual is always under the menace of new paroxysms. The increasing duration of the attacks with the appearance of signs of myocardial failure during the latest one is of prognostic significance.

### NOMOTOPIC TACHYCARDIA

Lewis [2] has defined paroxysmal tachycardia as an affection in which the heart rhythm (sino-atrial nodal rhythm) becomes submerged and the heart responds to impulses formed at a more rapid rate in some other portion of its walls. Such a definition precludes the conception of a nomotopic tachycardia and the later statement that paroxysms arising in the sino-atrial node have not as yet been identified follows as a corollary. Likewise, Mackenzie [3] states that paroxysmal tachycardia is a term to indicate the starting of the heart's contraction at an abnormal focus with a sudden increase in the rate of the heart. Donzelot,[4] in a study of the pathology of paroxysmal tachycardia, has included all exaggerated accelerations of the heart which begin and end abruptly. His classification embraces: (*a*) Regular paroxysmal tachycardia, which results from displacement of the stimulus, though he says it is possible to conceive the existence of a paroxysmal tachycardia, "normotope," but "heterotype." (*b*) Auricular tachysystole, atrial flutter. (*c*) Irregular paroxysmal tachycardia, atrial fibrillation. Wenckebach has described nomotopic tachycardia and recently G. Galli [5] reported a case with polygraphic records which he believed arose in the normal pacemaker, and has argued for nomotopic paroxsyms of neurogenic origin. Certain of his theses are worthy of criticism: I and IV. If vagus pressure is sufficient and prolonged it is usually successful in stopping the paroxysm: the Valsalva experiment reduces the

2. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, New York, Paul B. Hoeber, 1920.

3. Mackenzie, J.: Principles of Diagnosis and Treatment in Heart Affections, London, Oxford Press, 1916.

4. Donzelot, E.: Les Tachycardies Paroxystiques: Etude Pathogénique, Ann. de méd. **11**:155, 1914.

5. Galli, G.: Sur les Mécanisme de Terminaison et de Début des Accès dans la Tachycardie Paroxystique (Nomotope), Arch. d. mal. du coeur **12**:289, 1919.

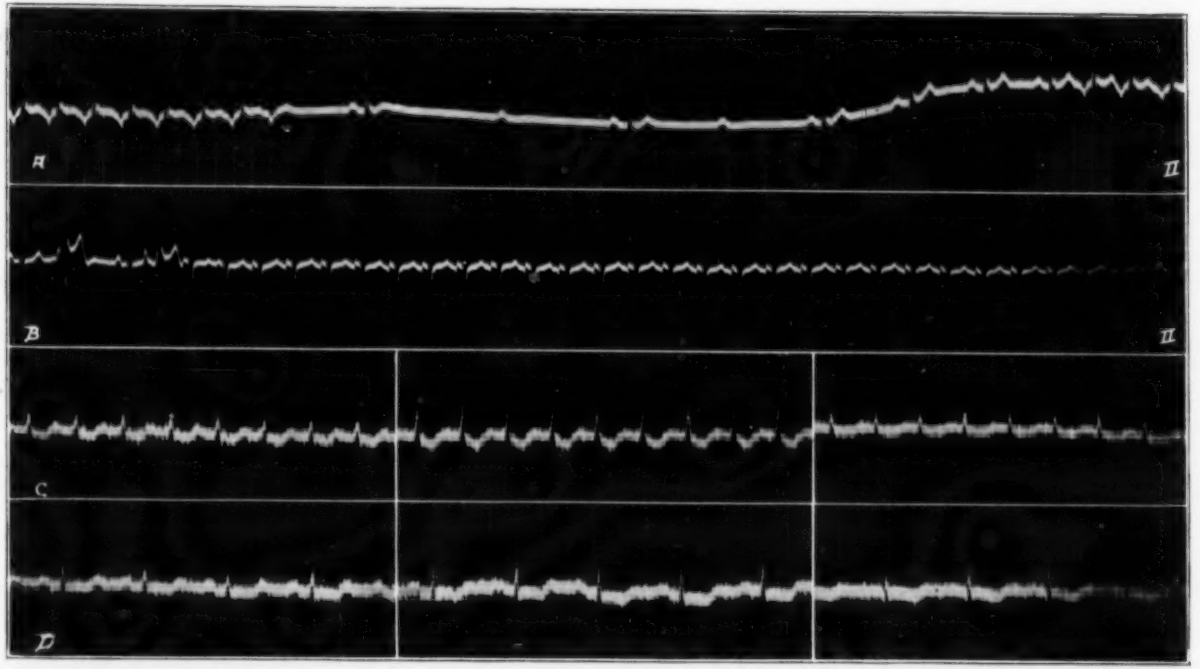


Plate 5.—A. Illustrating Case 4. Right vagus pressure applied fourteen cycles before first normal beat. B. Illustrating Case 5. C. Illustrating Case 6. About thirty-six hours after onset of paroxysm. D. Twenty-seven hours later, three hours after termination of paroxysm.

frequency of simple tachycardia and often arrests a paroxysm: those tachycardias not thus relieved are of heterotopic origin. The failure of vagus pressure on the basis of inadequate stimulation is difficult to answer. Surely but few continue vagus pressure for thirty minutes. The common practice is to apply pressure until the heart action is altered or the discomfort produced demands its discontinuance. It is the usual experience of those who resort to this procedure that in some cases it is apparently successful while in others there is no effect. In Case 1 of the present series the effect of vagus pressure was doubtful and in the case of Carter and Wedd [6] no pressure that could be endured influenced the paroxysm. On the other hand, there are numerous records of unquestioned heterotopic tachycardias which are definitely affected by stimulation, for example, Case 4. In Case 3 the patient had long successfully practiced the Valsalva experiment, but the effect of vagus pressure is difficult to interpret because of the recurring short paroxysms, and the fact that there was no change in the electrocardiogram. III. Atropin in sufficient dosage may induce a paroxysm of tachycardia. It did in Case 3, but the paroxysm arose at the A-V node, not the sinus node. V. An emotion may bring forth a paroxysm. But again, it may be a heterotopic rhythm, as in Case 3. VII. There occurs at times an abrupt passage from normal rhythms to that of simple tachycardia. This presupposes proof of the exact nature of both phases. From observation alone of the movements of the galvanometer string during the paroxysm in Case 1 that seemed to occur, but examination of the record showed that without any pause, the change in rate from 115 to 188 followed a shift of pacemaker to a higher level in the auricle, with prolongation of A-V conduction and other changes in the electrocardiogram. X. Rhythmic oscillations may occur during a paroxysm; this is characteristic of sinus activity. The slow mechanism in Case 1 is an A-V arrhythmia. It is not possible to deny that fluctuation might occur in nodal tachycardias, though this rarely, if ever, occurs in any marked degree. VIII. The electrocardiogram usually shows a negative P wave and shortened conduction time: but P is not always inverted even in cases of evident nodal rhythm: moreover the eye accustomed to the perusal of electrocardiograms may be occasionally deceived, and finally the electrocardiogram is often difficult to interpret and ambiguous. All this is admitted, and likewise the conclusion that because the electrocardiogram shows most tachycardias to be heterogenetic, it is unjust to insist that only extrasinusal tachycardias may occur. However, when the electrocardiogram fails to

6. Carter, E. P., and Wedd, A. M.: Report of a Case of Paroxysmal Tachycardia Characterized by Unusual Control of the Fast Rhythm, Arch. Int. Med. 22:571 (Oct.) 1918.

show the origin of the rhythm, to what shall one turn? Polygraphic records may be more simple of interpretation, but who shall vouch for their authority?

Shortly after the appearance of the paper by Galli, a case of paroxysmal tachycardia was reported by Boden [7] in which during the paroxysm, the P wave of the electrocardiogram was similar to that in the normal, but with an increase in negativity in the ventricular complex. After atropin the electrocardiogram was exactly like that during the paroxysm, though the rate increased to only 144 while that of the paroxysm was 170. This was interpreted as a case of nomotopic tachycardia resulting from dominance of the accelerator system. In the discussion of the case of paroxysmal tachycardia with voluntary control reported by Carter and Wedd, while the term nomotopic was not used, it was stated that there could be no ectopic focus wholly removed from neurogenic control which was responsible for the fast rhythm. More recently White [8] has considered this subject in a study of a case in which there were short "paroxysms," but no abrupt onset or offset in the rapid rhythm. The P wave remained upright and fell back on T and there were slight variations in the intervals between beats at the height of the paroxysm, the maximum rate of which was about 188. This was called "paroxysmal tachycardia, arising in or very near the sino-atrial node and not showing an absolutely abrupt onset or offset." From the definitions given and the work cited the existing confusion is apparent. In the light of Lewis' later work, closer relations between extra-systoles, paroxysmal tachycardia, flutter and fibrillation are indicated, and it may well be that Donzelot in his clinical classification five years ago wrote better than the experimental knowledge of the time warranted. But to introduce as a paroxysmal tachycardia an altered mechanism which is neither heterogenic, ectopic nor paroxysmal in the common clinical meaning of having an abrupt onset and offset, is to further complicate the situation by bringing into the category simple tachycardias.

As to the nature of paroxysms of tachycardia, the conclusion is inevitable (Lewis) that the paroxysm is composed of a series of extrasystoles. Extrasystoles definitely known to arise in either the S-A or A-V node are rare, though their possibility or existence is not denied. (The term "extrasystole" is here used following the terminology of Lewis. Theoretically, the only true extrasystole not an ectopic beat is an interpolated sinus extrasystole. Inasmuch as practically all so-called

7. Boden, E.: Uber den Einfluss der langen Herznerven auf die Form des Elektrocardiogramms in einen Fall von Paroxysmaler Tachycardie, Deutsch. Arch. f. klin. Med. **130**:249, 1919.

8. White, P. D.: Clinical Observations on Unusual Mechanisms of the Auricular Pacemaker, Arch. Int. Med. **25**:420 (May) 1920.

extrasystoles are in reality ectopic beats, it would simplify a discussion of heterogenetic impulses and clarify their inter-relation if the former term could be dropped from the literature.) The occurrence of ectopic beats in the tachycardias under consideration may be mentioned at this point. In Case 1 no isolated abnormal beats have ever been seen. In Case 2 ectopic beats arising in the left ventricle have been frequently recorded; the paroxysm, however, was probably of supraventricular origin. Nodal beats were frequent in Case 3 and often occurred in pairs. In Case 4 ectopic beats arising at a low level in the atrium were constantly present, often giving rise to a coupled rhythm and from the conformation of the curves it appeared that the paroxysm arose at the same focus. In Case 5, although both ventricular and atrial ectopic beats occurred, the only paroxysms recorded were of the atrial type. No ectopic beats have been noted in Case 6, but the patient was under observation only ten days. Paroxysms which arise in the A-V node are known. Case 3 affords another example. There is no difficulty in this case, likewise in Cases 4 and 5, in seeing the paroxysm as a succession of extrasystoles. If extrasystoles can occur in the sinus node what is there to prevent a series of them? And if increased irritability may occur abruptly in the A-V node resulting in a succession of beats that constitutes a paroxysm, what prevents such an accident at the sinus node? Doubtless the more complete, at least better known, regulatory mechanism at the sinus node is an important factor.

In any criteria for paroxysmal tachycardia it would seem well to insist that the essential characteristic of the new rhythm shall be its abrupt onset and termination. A recent observation is that of a woman of 50 years of age who had had a finger nail removed, with cocain for the local anesthetic. Following the operation the pulse rate increased to 160 and she thought that the rapid and forceful heart action came on suddenly as she was being helped into bed. The cardiac mechanism was watched with the galvanometer for two hours. The electrocardiogram at this time and later showed that the rapid rhythm arose at the sinus node. The systolic pressure varied between 200 and 185 and the diastolic remained at about 110. From subsequent observations it appeared that the normal pressure was 150/85. The rate remained quite constant for about three hours; vagus pressure produced temporary slowing but did not break the rhythm. It seemed for a time as though this might be a sino-atrial paroxysmal tachycardia, but after four hours the rate was 140 and after six hours 120; the next morning it was 100, and during the two following days varied between 80 and 124. In experimental accelerator stimulation sino-atrial rates from 150 to 250, and occasionally higher, have been obtained. In Case 1 the nodal rhythm following exercise reached the rate of 150. The par-

oxysms reported showed rates varying between 120 and 195. It is not necessary to consider any rhythm which shows neither displacement of the stimulus nor an abrupt beginning or ending as other than a simple tachycardia. Rate alone can have no place as a criterion for paroxysmal tachycardia.

The difficulties of establishing a nomotopic paroxysm by means of the electrocardiogram are manifold. It is necessary to consider, and to differentiate, if possible, not only the intrinsic changes that may accompany the new rhythm but changes that may be due to increase in rate, stimulation of the cardiac nerves or changes in chemical environment, associated with or dependent on either of the foregoing.[9] No analysis of the paroxysm is reliable unless the onset and termination have been recorded. The record of Boden is wanting in this respect. That of Galli need not be considered because of the inadequacy of polygraphic records. In Case 2, if one were to consider only the fully developed new rhythm, especially Lead II, it would not be difficult to establish a nomotopic tachycardia; the wave preceeding R could be regarded as P and the conduction time would be normal; the small thickening after R would be called T and the diminished size, likewise the notching and the widening of R would be attributed to alteration in nerve control or chemical environment. But the facts that after a brief respite the paroxysm invariably begins without an atrial wave, and that the definite wave between the spikes spaces accurately as a T wave, cannot be dismissed. Another possible interpretation is that the paroxysm arises in the upper part of the right branch of the bundle and independent atrial contractions occur at the same rate. But from consideration of all the facts, a nomotopic tachycardia is impossible. In Case 1 there is an abrupt onset of a rapid rhythm apparently with displacement of the pacemaker to a higher level, lengthening of A-V conduction from 0.08 to 0.16 second, a lower and narrower R wave and absence of T. As has been noted, the paroxysm of tachycardia is but one feature of a temporary but profound sympathetic stimulation. This question arises, are these changes in the electrocardiogram specific for the new rhythm, or are they the result of sympathetic stimulation acting on the original rhythm, an exaggeration of those seen after the earlier exercise. The inversion and disappearance of T has been seen before; the lowering of R and shortening of ventricular response may be due to the increase in rate. Sympathetic stimulation tends to decrease A-V conduction and increase in rate to prolong it. The fact that the conduction time in this first cycle is practically double that of the preceding is significant and the later lengthening may be associated with increased rate. If as

9. Mines, G. R.: On Dynamic Equilibrium in the Heart, J. Physiol. **46**: 349, 1913.

Lewis says the changes seen during the paroxysm are an intrinsic part of the new mechanism then this is a new rhythm arising at a higher level in the atrium and details suggest that its origin may be the S-A node. In the absence of authoritative criteria nomotopic paroxysmal tachycardia cannot be proved in clinical electrocardiograms, but to deny the possibility of the same is to deny to the sinus node properties of irritability and rhythmicity present in the A-V node, also a homogenetic centre, and other loci in the heart where these functions are normaliy present in less degree, and surely this requires proof.

### THE RÔLE OF THE EXTRINSIC NERVES

The relation of the extrinsic nerves to cardiac irregularities has been extensively investigated. The attempt to control paroxysms of tachycardia by vagus pressure has long been practiced. The actual effects are debatable. While there are those who believe the procedure infallible, according to Lewis either there is no effect or the new rhythm abruptly ends and the normal rhythm is resumed. In Case 1, in which vagus control might be expected, on one occasion the paroxysm stopped twenty cycles after the application of pressure; prolongation of conduction and failure of ventricular response occurred, a common result of vagus stimulation. But at another time the paroxysm terminated in an exactly similar way when no pressure was used and the patient made no effort to stop the paroxysm. The same mechanism was seen for the third time, when the individual held his breath to stop the attack. In the case of Carter and Wedd, likewise a possible nomotopic tachycardia, there was lengthening of the P-R interval of the last cycle and failure of ventricular response terminated the paroxysm, although this could not be brought about by vagus pressure. It would seem in these two cases, both of which were due to predominant accelerator action, as though the normal rhythm was restored by a resumption of vagal tone, but that this did not occur as the result of interference from without. In Case 3, in which the paroxysms were definitely of sympathetic origin, one paroxysm continued for fifty-nine beats, being of longer duration than many, and ended abruptly without any change in the electrocardiogram. In Case 4, an atrial tachycardia, vagus pressure did apparently break the ectopic rhythm by the production of block.

The accelerator system has likewise received much attention. Bouveret [10] in 1889, from two cases of his own and from similar ones in the literature, described the malady that has since borne his name, essential paroxysmal tachycardia, which occurred in individuals said to be free from any disease of the heart, thyroid or central nervous system.

10. Bouveret, L.: De la Tachycardie Essentielle Paroxystique, Rev. de méd. **9**:753, 1889.

Because of normal findings in the intervals between attacks he argued that the trouble must come from a profound disturbance in the innervation of the heart and believed that the mechanism was by excitation of the accelerator nerves, probably in the intracardiac ganglia. The etiology included a combination of physical and cerebral causes; physical fatigue, emotion and sense of cold were given as precipitation causes of the paroxysms. Rothberger and Winterberg,[11] studying the effect of stimulation of the accelerator nerves and sympathetic ganglia, found the usual reaction to be a simple tachycardia with characteristic changes in the electrocardiogram; in one instance after stimulation of the left accelerator a negative atrial wave appeared without increase in frequency; following simultaneous stimulation of both accelerators T almost entirely disappeared and when present was a negative wave. In a later work they produced a heterotopic tachycardia by sympathetic stimulation in a heart previously treated with barium chlorid. Donzelot reported extrasinusal or heterotopic tachycardias from stimulation of the left stellate ganglion. Levy [12] has shown the occurrence of ectopic ventricular beats after accelerator stimulation in cats which were under light chloroform anesthesia. Clerc and Pezzi [13] obtained heterotopic tachycardias arising in various levels of the A-V node after excitation of the accelerator nerves, but instead of faradic stimulation, they resorted to strontium chlorid and nicotin for exciting agents. The conclusion of Lewis from his consideration of experimental and clinical cases is that it has not been shown that abnormal nerve impulses playing upon a normally nourished heart may be responsible for extrasystoles or higher types of disorders, but that nervous impulses playing upon an irritable heart may provoke such reactions.

Galli [14] recently reported a case in which paroxysms are said to have come on after atropin, and which he believed to be conclusive evidence of vagus control of the paroxysm. Lewis emphasizes the fact that this occurred in a patient subject to paroxysms. Moreover, in this case the small dose of atropin generally given and the delayed response cast some doubt on the atropin effect. One mg. hypodermically is a small dose, and the tachycardia did not develop for forty-three minutes. The atropin effect ordinarily has begun to wear away by this time. The only convincing record is that in his Figure 5, in which the paroxysm came on fifty minutes after the administration of 30 drops by mouth

11. Rothberger and Winterberg: Ueber die Beziehungen der Herznerven zur Form des Elektrocardiogramms, Arch. f. d. ges. Physiol. **135**:506, 1910.
12. Levy, A. G.: The Exciting Causes of Ventricular Fibrillation in Animals under Chloroform Anesthesia, Heart **4**:319, 1912.
13. Clerc, A., and Pezzi, C.: Le Rythme Septal du Coer, Arch. d. mal. du coeur **13**:103, 1920.
14. Galli, G.: Attacks of Paroxysmal Tachycardia Following Atropin, Heart, **7**:111, 1920.

and persisted for two and one-quarter hours, and here it is the comparative duration that is important. In Case 3 of this series shortly after the administration of 2 mg. atropin a paroxysm occurred at a higher rate than the spontaneous paroxysms, and persisted without interruption for four hours, during which time no usually successful maneuvers would stop it. The higher rate in this paroxysm may have been due to the fact that although the spontaneous paroxysms resulted from heightened accelerator action the vagus still exerted some influence, which was removed by atropin. That a slight mental disturbance occurred may have indicated unusual susceptibility to this drug, but the cardiac response was such as to leave no doubt that the abolition of vagus tone was a definite factor in the long paroxysm.

The position of Lewis, which postulates an underlying toxemia rendering the heart abnormally susceptible to unusual activity of the extrinsic nerves, is incontrovertible, for who can prove that there is no subtle poison at work. It remains to inquire into the possible nature of the toxins. Danielopolu,[15] accepting the doctrine that paroxysmal tachycardia cannot originate in an intact myocardium, described an interesting case of exophthalmic goiter in which there were paroxysms of tachycardia associated with unilateral exophthalmos. According to his explanation, simultaneous stimulation of both accelerators occurred, that of the right gave rise to the exophthalmos and the left, to a heterotopic tachycardia. For the latter he assumed a lesion in the bundle of His which was in a hyperexcitable state and the toxic product of the thyroid gland acted as the exciting agent. A few cases of paroxysmal tachycardia have been reported in which histologic findings were negative, and in the case of thyroid disease it does not appear necessary to presuppose an organic lesion; moreover, this is unlikely in the early stages of the disease. Besides the affections attributed more or less definitely to the thyroid there remains the entire gamut of disorders of the autonomic nervous system. Cases 1 and 3 of this series hardly fit into any of the groups included under exophthalmic goiter or in that of the irritable heart, nor is there sufficient reason to believe that early organic heart disease exists. In the first case the paroxysm is only an incident in the violent reaction to sudden sympathetic stimulation; the drenching sweats are the outstanding feature for the patient. In the other case, the dilated pupils, sweating palms, dermographia and unstable cardiac mechanism constitute a familiar clinical picture, of which the paroxysms so easily provoked are only a part. But these individuals belong somewhere among the confused syndromes called

15. Danielopolu, D.: Accés de Tachycardie Paroxystique avec Exophthalmie Unilaterale chez une Ancienne Basedowienne, Compt. rend. Soc. de biol. **79**: 103, 1916.

endocrinopathies. It is hardly advisable to emphasize Case 6 in this connection, except to recall that there is a definite history of paroxysms of tachycardia extending over a period of forty-three years and that even today there is no demonstrable evidence of heart disease in the usual meaning of that term, and to suggest that this patient belongs to the same group. In such conditions is not the consideration of toxic substances rendering centers abnormally susceptible to nervous influence which precipitate the disturbances merely calling one thing by two names, or perhaps attempting to push the question further back into the chemical pathology of the autonomic system? And may it not be that when this pathology shall be understood, there will stand one group of paroxysmal tachycardias due to faulty nervous control as Bouveret has written, the fault being whatever may come to be recognized as pathologic in the autonomic nervous system?

SUMMARY

Six cases of paroxysmal tachycardia are reported. Two are in elderly individuals in whom there are signs of degenerative changes involving the heart and aorta. This is a frequent association and the paroxysms are believed to be expressions of high irritability in inflammatory foci in the muscle wall. A third case is an example of a group of paroxysmal tachycardias that are usually considered to be of reflex origin. The visceroptosis and alimentary stasis are of long standing. The recent appearance of paroxysms where formerly ectopic beats alone occurred indicates an altered response on the part of the heart. The direct relation between the paroxysms and the alimentary condition is apparent and suggests that the paroxysms are analagous to those produced by ligation of the coronary arteries; because of mechanical displacement embarrassment of the coronary circulation results and there may have occurred changes in the heart muscle, not detectable by physical signs, which render the myocardium less tolerant of interference with its blood supply. Three of the cases seem to fulfill the requirements of the "maladie de Bouveret." There is no evidence of organic heart disease, nor of Graves' disease or so-called hyperthyroidism. The two young men are suffering from some disorder of the autonomic nervous system in which transient predominance of the accelerator division frequently occurs. In this connection the rôle of the extrinsic nerves of the heart in paroxysms of tachycardia has been considered, and it is believed unnecessary to postulate the existence of an underlying toxemia which renders the heart abnormally susceptible to nerve impulses, for both of these factors may well be one and the same thing, and it is hardly necessary at present to attempt to differentiate neuro- from chemical pathology in the autonomic nervous system.

Concerning nomotopic paroxysmal tachycardia there is much confusion in the literature and the most authoritative definitions of paroxysmal tachycardia do not include even the possibility of its existence. It is suggested that the first requirement of any paroxysm shall be an abrupt onset and termination. The necessity of recording the onset of a paroxysm for its correct analysis has been pointed out. In the first case reported, in which the dominant rhythm has its origin in the A-V node, with the onset of the paroxysm there was a sudden shifting of the pacemaker to a higher level in the atrium and from the character of the electrocardiogram the new rhythm might have originated in the S-A node. However, nomotopic tachycardia cannot be established by clinical electrocardiograms. Paroxysms of tachycardia are now regarded as successions of extrasystoles. The existence of sinus extrasystoles is recognized. But even in the absence of demonstrable relationship between such beats and the paroxysm in any given case the negation of the possibility of a nomotopic paroxysmal tachycardia does not seem justifiable.

# IRON AND ARSENIC AS INFLUENCING BLOOD REGENERATION FOLLOWING SIMPLE ANEMIA

## VI. NEGATIVE INFLUENCE OF FAMILIAR DRUGS ON THE CURVE OF HEMOGLOBIN REGENERATION FOLLOWING HEMORRHAGE *

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Is iron of value in the treatment of anemia? Is iron absorbed from the intestine when given in organic or inorganic form? Such questions lead to fields of discussion over which has risen the smoke of polemics and arguments without end. We believe that some of these difficulties may be cleared away by careful definition of terms. Our experiments deal with secondary anemia due to hemorrhage and not with chlorosis or any other form of anemia. We have controlled certain diet factors which can influence profoundly the hemoglobin regeneration in this form of secondary anemia. We suggest that our critics control these diet factors before any great emphasis is placed upon drug factors. It is now established that diet factors are concerned in the rapid regeneration of hemoglobin, therefore, these facts must be considered in evaluating any reaction in conditions of anemia.

Chlorosis has been mentioned so frequently in this discussion and others that we feel it necessary to state that in our opinion this condition does not belong in this group of simple secondary anemias. Whether this disease reacts favorably to iron therapy is not germane to this discussion. It seems to be a disease which is becoming much less frequent in many communities due to modified dietary or living conditions or other unknown factors. It would be of interest to collect accurate data on the influence of diet factors alone in this disease.

We do not think it is necessary to review the literature of anemia and iron therapy. It may be admitted that we have not tested all the various forms of iron which are being used in the treatment of anemia, but it seems to us that this is not necessary. We are able to show that many of the iron preparations commonly prescribed are inert, or, at least, much less potent than simple diet factors. The burden of proof now rests with those who claim that one or more iron preparations are potent in anemia under controlled diet conditions.

Some experimental work has been done in secondary anemia to show whether or not iron compounds are potent in stimulating the regenera-

* From the George Williams Hooper Foundation for Medical Research, University of California Medical School.

tion of hemoglobin. In much of this work the anemia was produced by drugs which destroy the red cells in the body and leave the freed hemoglobin to be stored or used in any way by the endogenous body mechanism. This type of anemia must not be confused with the type used in our experiments—that is, anemia due to simple hemorrhage. This destruction of red cells in the body may be associated with a storage of hemoglobin radicles somewhere in the body which may be capable of influencing subsequent hemoglobin regeneration. We hope to report on this type of hemoglobin regeneration in the near future.

Arsenicals were used in some of our experiments. It seemed best to include some of this group in this paper because their use in certain forms of anemia is well recognized. Both Fowler's solution and sodium cacodylate are inert under the conditions of these experiments.

Objection may be raised to the use of dogs in these experiments because they are carnivorous animals. The dogs used by us were raised in our kennels and have been omnivorous since weaning. The diet on which they thrive is a mixture of food scraps obtained from the University Hospital. It contains cooked bones, meat, bread, potatoes, rice, etc. This mixed diet obtains in all resting periods between experiments. Unless otherwise noted, these animals are active, healthy and normal in all respects.

## EXPERIMENTAL OBSERVATIONS

The general method used in all these experiments has been fully discribed in the first paper of this series.[1] Unless otherwise stated, the plasma volume has been directly determined by the nontoxic dye, "brilliant vital red."[2] This dye has been furnished us through the courtesy of Dr. H. M. Evans of the department of anatomy, and we are indebted to him for much advice and council. The blood is received into isotonic sodium oxalate solution, and the ratio of cells and plasma is determined in calibrated centrifuge tubes. The hemoglobin is determined by a modification of the Palmer method described recently by one of us (F.S.R.).[3] Red and white counts are made in the usual manner from blood obtained by venous puncture. For other details of this work, we refer the reader to the first paper of this series.[1]

Paper V of this series[4] records many experiments in which Blaud's pills were added to various diets. We wish to refer to this paper for the details of these experiments. Blaud's pills were inert under these experimental conditions. It seemed necessary to test out other drugs

1. Whipple, Hooper and Robscheit: Am. J. Physiol. **53**:151, 1920.
2. Hooper, Smith, Belt and Whipple: Am. J. Physiol. **51**:205, 1920.
3. Robscheit: J. Biol. Chem. **41**:209, 1920.
4. Hooper, Robscheit and Whipple: Am. J. Physiol. **53**:263, 1920.

under these same conditions, and the charts giving these data are given below.

TABLE 82.—BLOOD REGENERATION—FERRIC CITRATE

Dog 18-114. Bull mongrel. Female. Adult

| Date, 1919 | Pigment Volume Hb. per Cent. Times Blood Volume | Blood Volume | Plasma Volume | R. B. C. Volume | R. B. C. Hematocrit | Hb. | Color Index | R. B. C., Million | W. B. C. | Weight | Blood per Kilogram | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C.c. | C.c. | C.c. | % | % | | | | Kg. | C.c. | |
| 7/ 8 | 2,078 | 1,625 | 754 | 854 | 52.4 | 128 | 0.72 | 8,8 | 12,4 | 12.25 | 132 | |
| 7/ 8 | Diet: Bread and milk | | | | | | | | | | | |
| 7/ 9 | Bled 406 c.c. | | | | | | | | | | | |
| 7/10 | Bled 406 c.c. | | | | | | | | | | | |
| 7/12 | 805 | 1,262 | 802 | 348 | 27.6 | 64 | 0.82 | 3,9 | 8,2* | 11.95 | 105 | |
| 7/12 | Diet: 150 gm. bread, 500 c.c. milk, 1 c.c. of 5% solution of ferric citrate subcutaneously daily | | | | | | | | | | | |
| 7/20 | 1,188 | 1,383 | 858 | 491 | 35.5 | 86 | 0.94 | 4,6 | 12,2 | 11.95 | 115 | |
| 7/28 | 1,215 | 1,380 | 826 | 520 | 37.6 | 88 | 0.80 | 5,5 | 9,8 | 11.70 | 118 | * Slight |
| 8/ 3 | 1,225 | 1,340 | 822 | 523 | 39.0 | 91 | 0.79 | 5,8 | 9,0 | 11.50 | 116 | * Slight |
| 8/13 | 1,130 | 1,410 | 846 | 544 | 38.5 | 80 | 0.73 | 5,6 | 8,2 | 11.65 | 121 | * Slight |
| 8/20 | 1,344 | 1,325 | 768 | 574 | 43.3 | 101 | 0.85 | 6,0 | 7,4 | 11.35 | 117 | * Slight |
| 8/27 | 1,498 | 1,440 | 772 | 646 | 44.9 | 104 | 0.84 | 6,2 | 11,0 | 11.20 | 128 | * Slight |
| 9/ 3 | 1,428 | 1,498 | 850 | 629 | 42.0 | 95 | 0.75 | 6,3 | 10,4 | 11.05 | 135 | * Polk. |
| 9/10 | 1,405 | 1,388 | 774 | 599 | 43.2 | 101 | 0.80 | 6,3 | 8,4 | 10.65 | 130 | * Polk. |
| 9/10 | Diet: Mixed, with extra food. (No ferric citrate given) | | | | | | | | | | | |
| 9/17 | 1,693 | 1,693 | 985 | 691 | 40.8 | 100 | 0.73 | 6,9 | 6,4 | 13.55 | 125 | * Polk.+† |
| 9/24 | 1,653 | 1,598 | 1,053 | 722 | 40.1 | 92 | 0.73 | 6,3 | 6,8 | 15.00 | 120 | * Polk.+† |

* Poikilocytosis of red blood cells.
† Food poor in meat.

Table 82 shows the curve of blood regeneration of a standard dog on a bread and milk diet given ferric citrate subcutaneously. It may be stated that the same reaction would be expected in the same dog under identical conditions without the ferric citrate. We can refer to other experiments on this same dog which show the expected favorable and rapid blood regeneration on diets of meat and liver. Table 49 of this series [5] shows the curve of blood regeneration on a diet of cooked meat scraps. The return to normal was almost complete in three weeks. Also Table 61 of this series [6] shows the curve of blood regeneration on a diet of cooked beef liver. The return to normal was complete in two weeks and somewhat above the initial level in three weeks.

This favorable blood regeneration on this diet of meat or liver is in contrast to the slow reaction expected on bread and milk or actually recorded in Table 82 with bread and milk plus ferric citrate.

5. Whipple, Robscheit and Hooper: Am. J. Physiol. **53**:238, 1920.
6. Whipple, Robscheit and Hooper: Am. J. Physiol. **53**:252, 1920.

Several interesting points in this experiment should be noted. The blood per kilo is a very high figure, on the average. This is usually found in very active dogs which are somewhat below normal in weight. This dog lost some weight during the bread and milk feeding and the plasma volume likewise decreased as is common under such conditions. This accounts, in part, for some of the increase in red hematocrit and hemoglobin, but is more accurately evaluated in the pigment volume figures. When the dog is put on forced feeding, there is a remarkable gain in weight and plasma volume and an actual fall in red hematocrit and hemogoblin. The pigment volume, however, shows the true values for hemoglobin production. A hasty survey of these figures might lead one to erroneous conclusions unless the facts as given are carefully weighed. This type of experiment shows, too, the necessity of blood plasma measurements.

TABLE 83.—Blood Regeneration—Ferric Citrate

Dog 19-95. Bull mongrel. Male. Adult

| Date, 1920 | Pigment Volume Hb. per Cent. Times Blood Volume | Blood Volume | Plasma Volume | R. B. C. Volume | R. B. C. Hematocrit | Hb. | Color Index | R. B. C., Million | W. B. C. | Weight | Blood per Kilogram | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C.c. | C.c. | C.c. | % | % | | | | Kg. | C.c. | |
| 7/ 8 | 1,570 | 1,412 | 754 | 644 | 45.6 | 111 | 0.79 | 7.0 | 7.4 | 12.25 | 115 | * Slight |
| 7/ 8 | Diet: Bread and milk | | | | | | | | | | | |
| 7/ 9 | Bled 353 c.c. | | | | | | | | | | | |
| 7/10 | Bled 353 c.c. No distress | | | | | | | | | | | |
| 7/12 | 722 | 1,062 | 741 | 301 | 28.6 | 68 | 0.86 | 4.0 | 11.0 | 12.05 | 87 | * Slight |
| 7/12 | Diet: 150 gm. bread, 500 c.c. milk, 1 c.c. of 5% solution ferric citrate subcutaneously daily | | | | | | | | | | | |
| 7/20 | 1,133 | 1,295 | 814 | 469 | 36.2 | 87 | 0.87 | 5.0 | 12.2 | 11.80 | 110 | * Slight |
| 7/28 | 1,190 | 1,264 | 749 | 508 | 40.2 | 94 | 0.78 | 6.0 | 10.8 | 11.80 | 107 | * Slight |
| 8/ 3 | 1,256 | 1,256 | 702 | 542 | 43.2 | 100 | 0.84 | 6.0 | 7.2 | 11.75 | 107 | * Slight |
| 8/13 | 1,141 | 1,197 | 672 | 513 | 42.9 | 95 | 0.79 | 6.0 | 17.0 | 11.75 | 102 | * Slight |
| 8/20 | 1,215 | 1,225 | 711 | 502 | 41.0 | 99 | 0.85 | 5.8 | 12.0 | 11.55 | 106 | * Slight |
| 8/27 | 1,185 | 1,212 | 695 | 505 | 41.7 | 98 | 0.71 | 6.9 | 5.8 | 11.65 | 104 | * Poik. + |
| 9/ 3 | 1,273 | 1,308 | 730 | 561 | 43.0 | 98 | 0.72 | 6.8 | 6.4 | 11.50 | 113 | * Poik. + |
| 9/10 | 1,165 | 1,202 | 709 | 481 | 40.0 | 97 | 0.81 | 6.0 | 7.2 | 11.35 | 106 | * Poik. + |
| 9/10 | Diet: Mixed, with extra meat. (No ferric citrate given) | | | | | | | | | | | |
| 9/17 | 1,632 | 1,497 | 808 | 674 | 45.0 | 109 | 0.82 | 6.6 | 6.6 | 13.75 | 109 | * Slight |

* Poikilocytosis of red blood cells.

Table 83 shows the influence of ferric citrate given subcutaneously. We are able to refer to other experiments on this same animal which have been published. Table 3 of this anemia series [7] gives the curve of blood regeneration on a mixed diet. It is clear in this experiment

7. Whipple, Hooper and Robscheit: Am. J. Physiol. **53**:159, 1920.

that blood regeneration was slow until meat was added in liberal amounts. The curve of regeneration finally returned to normal. Table 41 gives the blood regeneration curve on a liberal diet of rice, potatoes and milk. It is clear that these curves, if anything, are better than the curve of Table 83. We have established the fact that this rice-potato-milk diet is slightly more favorable for blood regeneration than a simple bread and milk diet.

These control experiments under identical conditions make it clear that the ferric citrate under these experimental conditions is inert. The curve of regeneration has not been influenced by the administration of this drug.

TABLE 84.—Blood Regeneration—Ovoferrin

Dog 20-3. Bull mongrel. Male. Adult

| Date, 1919 | Pigment Volume = Hb. per Cent. Times Blood Volume | Blood Volume | Plasma Volume | R. B. C. Volume | R. B. C. Hematocrit | Hb. | Color Index | R. B. C., Million | W. B. C. | Weight | Blood per Kilogram | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C.c. | C.c. | C.c. | % | % | | | | Kg. | C.c. | |
| 7/29 | 1 588 | 1,495 | 766 | 715 | 47.8 | 106 | 0.77 | 6,9 | 7,6 | 13.60 | 110 | * Slight |
| 7/29 | Diet: Bread and milk | | | | | | | | | | | |
| 7/30 | Bled 374 c.c. | | | | | | | | | | | |
| 7/31 | Bled 374 c.c. | | | | | | | | | | | |
| 8/ 2 | 634 | 1,177 | 884 | 281 | 23.9 | 54 | 0.69 | 3,9 | 8,2 | 13.05 | 90 | * Slight |
| 8/ 3 | Diet: 150 gm. bread, 500 c.c. milk, 1 teaspoonful ovoferrin daily | | | | | | | | | | | |
| 8/13 | 1,065 | 1,287 | 784 | 490 | 38.1 | 83 | 0.81 | 5,1 | 8,6 | 12.35 | 104 | * Slight |
| 8/13 | Diet: 150 gm. bread, 500 c.c. milk, 2 teaspoonfuls ovoferrin daily | | | | | | | | | | | |
| 8/20 | 1,148 | 1,247 | 750 | 490 | 39.3 | 92 | 0.79 | 5,8 | 7,8 | 12.30 | 102 | * Slight |
| 8/27 | 1,057 | 1,185 | 706 | 468 | 39.5 | 89 | 0.75 | 5,9 | 6,6 | 11.65 | 102 | * Slight |
| 9/ 3 | 1,075 | 1,273 | 783 | 477 | 37.5 | 84 | 0.96 | 4,9 | 6,4 | 11.55 | 110 | * Slight |
| 9/ 3 | Diet: Mixed, with extra food (meat ++). No ovoferrin | | | | | | | | | | | |
| 9/10 | 1,180 | 1,382 | 896 | 475 | 34.4 | 85 | 0.85 | 5,0 | 6,6 | 13.00 | 106 | * Slight |
| 9/17 | 1,410 | 1,658 | 1,053 | 588 | 35.5 | 80 | 0.83 | 5,1 | 6,2 | 15.00 | 110 | * Slight |
| 9/24 | 1,915 | 1,982 | 1,120 | 842 | 42.5 | 97 | 0.83 | 5,8 | 6,4 | 16.80 | 118 | |

* Poikilocytosis of red blood cells.

Table 84 may, at first sight, be favorable to ovoferrin as influencing the curve of blood regeneration. On careful analysis, however, we note very little, if any, change which may be attributed to the drug. Compare Table 84 with Table 92, an experiment of similar type during which sodium cacodylate was administered. There is little difference in reaction. Another experiment on this same dog is recorded (Table 86) in which a salt mixture containing a small amount of iron was given. This salt mixture seems to exert a somewhat favorable influence—a much more decided influence than the iron alone. Therefore, this minimizes the actual influence of the iron on the hemoglobin regen-

eration. The ovoferrin (Ferri vitellinum syntheticum) was obtained from the University Hospital.

Table 84 shows a sharp jump in hemoglobin, red hematocrit and pigment volume during the first ten days following the double bleeding. This is often observed after two bleedings, and has less significance than when following three bleedings, which tend to lessen this "reserve factor." We believe this reaction has little relation to the drug. During the next three weeks on the drug the pigment volume remains unchanged, although there are slight fluctuations in red hematocrit and hemoglobin. This means that the "maintenance factor" alone is being supplied. A change to a heavy mixed diet with cooked meat brings about little change in hemoglobin and hematocrit values, but the great gain in weight is associated with much increase in blood volume and actually the pigment volume gives the true picture which is a rapid increase in actual amount of formed hemoglobin in the body. The pigment volume almost doubles in this short period, associated with a gain in weight of 5 kilos. This shows again the necessity of blood volume measurement in work of this sort and shows the comparative value of iron and meat as influencing hemoglobin formation in the body under these conditions. We can attribute little value to the drug but the meat diet at once shows a striking reaction.

TABLE 85.—Blood Regeneration—Ovoferrin

Dog 20-2. Bull mongrel. Male. Young adult

| Date, 1930 | Pigment Volume = Hb. per Cent. Times Blood Volume | Blood Volume | Plasma Volume | R. B. C. Volume | R. B. C. Hematocrit | Hb. | Color Index | R. B. C., Million | W. B. C. | Weight | Blood per Kilogram | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C.c. | C.c. | C.c. | % | % | | | | Kg. | C.c. | |
| 7/29 | 2,001 | 1,715 | 796 | 904 | 52.6 | 117 | 0.79 | 7.4 | 7.2 | 15.15 | 113 | * Slight |
| 7/29 | Diet: Bread and milk | | | | | | | | | | | |
| 7/30<br>7/31 | Bled 430 c.c.<br>Bled 430 c.c. | | | | | | | | | | | |
| 8/ 2 | 898 | 1,261 | 863 | 392 | 31.1 | 71 | 1.10 | 3.2 | 6.8 | 14.45 | 87 | |
| 8/ 3 | Diet: 150 gm. bread, 500 c.c. milk, 1 teaspoonful ovoferrin daily | | | | | | | | | | | |
| 8/13 | 1,310 | 1,447 | 803 | 638 | 44.1 | 90 | 0.74 | 6.1 | 6.0 | 14.05 | 103 | |
| 8/13 | Diet: 150 gm. bread, 500 c.c. milk, 2 teaspoonfuls ovoferrin daily | | | | | | | | | | | |
| 8/20 | 1,512 | 1,429 | 786 | 636 | 44.5 | 106 | 0.88 | 6.0 | 6.8 | 13.75 | 104 | * Slight |
| 8/27 | 1,430 | 1,430 | 780 | 636 | 44.5 | 100 | 0.77 | 6.5 | 5.2 | 13.65 | 105 | * Slight |
| 9/ 3 | 1,670 | 1,585 | 774 | 742 | 48.3 | 100 | 0.72 | 7.6 | 6.0 | 13.85 | 113 | * Slight |
| 9/10 | 1,523 | 1,419 | 744 | 661 | 46.6 | 107 | 0.85 | 7.2 | 6.4 | 13.20 | 107 | * Slight |
| 9/17 | 1,666 | 1,445 | 765 | 698 | 46.3 | 111 | 0.83 | 6.7 | 5.8 | 13.20 | 109 | * Slight |
| 9/17 | Diet: Mixed.† No ovoferrin | | | | | | | | | | | |
| 9/24 | 1,858 | 1,795 | 965 | 822 | 45.8 | 104 | 0.80 | 6.5 | 6.0 | 16.00 | 112 | * slight |

* Poikilocytosis of red blood cells.
† Food poor in meat.

Table 85 shows a somewhat favorable reaction following two bleedings. The anemia level in this experiment was not sufficiently reduced, and a reaction of this type would be expected on bread and milk alone. Compare this experiment with another on the same dog (Table 90) using Fowler's solution. The change in blood volume is striking when the dog is put on a liberal mixed diet and the corresponding adjustment of hemoglobin and hematocrit values is of interest.

TABLE 86.—BLOOD REGENERATION—SALT MIXTURE *

Dog 20-3. Bull mongrel. Male. Adult

| Date, 1919 | Pigment Volume Hb. per Cent. Times Blood Volume | Blood Volume | Plasma Volume | R. B. C. Volume | R. B. C. Hematocrit | Hb. | Color Index | R. B. C., Million | W. B. C. | Weight | Blood per Kilogram | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C.c. | C.c. | C.c. | % | % | | | | Kg. | C.c. | |
| 10/27 | 1,500 | 1,478 | 736 | 721 | 48.8 | 129 | 0.93 | 6.9 | 8.8 | 16.55 | 89 | |
| 10/27 | Diet: Bread and milk | | | | | | | | | | | |
| 10/28 | Bled 370 c.c. | | | | | | | | | | | |
| 10/29 | Bled 370 c.c. No distress | | | | | | | | | | | |
| 10/31 | 778 | 1,045 | 732 | 308 | 29.0 | 74 | 0.95 | 3.9 | 22.6 | 15.55 | 67 | |
| 10/31 | Bled 261 c.c. | | | | | | | | | | | |
| 11/ 3 | 661 | 1,060 | 740 | 271 | 26.3 | 64 | 0.97 | 3.3 | 16.8 | 15.35 | 67 | |
| 11/ 3 | Diet: 175 gm. bread, 2 gm. salt mixture,* 500 c.c. milk | | | | | | | | | | | |
| 11/13 | 1,090 | 1,160 | 697 | 454 | 39.1 | 94 | 0.89 | 5.3 | 9.2 | 15.50 | 75 | |
| 11/20 | 1,580 | 1,421 | 765 | 643 | 45.2 | 111 | 0.76 | 7.3 | 9.0 | 15.30 | 93 | † Slight |
| 11/26 | 1,548 | 1,421 | 711 | 697 | 49.0 | 109 | 0.68 | 8.0 | 8.0 | 14.75 | 96 | † Slight |
| 12/ 3 | 1,545 | 1,400 | 700 | 686 | 49.0 | 110 | 0.68 | 8.1 | 6.8 | 14.70 | 95 | † Slight |
| 12/10 | 1,666 | 1,436 | 718 | 706 | 49.1 | 116 | 0.68 | 8.5 | 6.8 | 14.35 | 100 | † Slight |
| 12/17 | 1,445 | 1,343 | 674 | 656 | 48.8 | 108 | 0.74 | 7.3 | 7.4 | 14.15 | 95 | † Slight |
| 12/24 | 1,474 | 1,333 | 566 | 654 | 49.0 | 110 | 0.65 | 8.4 | 13.6 | 14.00 | 95 | † Poik. ++ |

Beginning dietary deficiency disease. Recovery.

* Salt mixture No. 185 (McCollum and Simmonds:* NaCl, 8.65 gm.; $MgSO_4$ (anhydrous), 13.30 gm.; $NaH_2PO_4H_2O$, 17.35 gm.; $K_2HPO_4$, 47.70 gm.; $CaH_4(PO_4)_2H_2O$, 27.00 gm.; Fe citrate, 5.9 gm.; Ca lactate, 65.0 gm. Iron equivalent to 64 mg. or 0.96 gm. daily.

† Poikilocytosis of red blood cells.

Tables 86, 87 and 88 show experiments which are much alike but present minor differences. This salt mixture (McCollum and Simmonds) contains per 2 gm. dose ferric citrate amounting to 64 mg. We note, in general, a somewhat more favorable reaction than is to be expected on this same diet without the salt mixture. This reaction is much like that observed on a liberal diet of rice, potatoes and milk. The regeneration during the first two weeks is quite rapid, but the return to normal is never complete, and the dogs show little change during subsequent weeks, the hemoglobin, red hematocrit and pigment volume showing minor fluctuations but remaining subnormal. It may well be debated that this favorable reaction is not to be attributed to the iron salts but to one or another of the many salts in this mixture. We

hope to make observations on the influence of various salt mixtures with and without iron, both organic and inorganic.

Two dogs developed a characteristic dietary deficiency disease after a period of several weeks. This condition will be discussed at length in a future publication.

TABLE 87.—Blood Regeneration—Salt Mixture †

**Dog 20-1. Bull mongrel. Female. Adult**

| Date, 1919 | Pigment Volume = Hb. per Cent. Times Blood Volume | Blood Volume | Plasma Volume | R. B. C. Volume | R. B. C. Hematocrit | Hb. | Color Index | R. B. C., Million | W. B. C. | Weight | Blood per Kilogram | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C.c. | C.c. | C.c. | % | % | | | | Kg. | C.c. | |
| 10/27 | 1,744 | 1,339 | 647 | 692 | 50.6 | 122 | 0.89 | 7,4 | 12,4 | 13.75 | 96 | |
| 10/27 | Diet: Bread and milk | | | | | | | | | | | |
| 10/28 | Bled 330 c.c. No distress | | | | | | | | | | | |
| 10/29 | Bled 330 c.c. No distress | | | | | | | | | | | |
| 10/31 | 848 | 1,072 | 732 | 330 | 30.8 | 79 | 1.01 | 3,9 | 28,6 | 13.35 | 80 | |
| 11/ 1 | Bled 268 c.c. | | | | | | | | | | | |
| 11/ 1 | 617 | 984 | 712 | 252 | 25.7 | 68 | 1.10 | 2,8 | 22,0 | 12.00 | 76 | |
| 11/ 2 | Diet: 200 gm. bread, 2 gm. salt mixture,† 500 c.c. milk | | | | | | | | | | | |
| 11/13 | 898 | 984 | 596 | 377 | 38.3 | 91 | 0.80 | 5,7 | 9,6 | 12.50 | 79 | |
| 11/20 | 1,306 | 1,120 | 570 | 540 | 48.2 | 117 | 0.68 | 8,6 | 5,2 | 12.10 | 93 | |
| 11/22 | Diet: 150 gm. bread, 2 gm. salt mixture, 500 c.c. milk | | | | | | | | | | | |
| 11/26 | 1,396 | 1,255 | 605 | 638 | 50.8 | 111 | 0.65 | 8,6 | 5,8 | 11.80 | 106 | |
| 12/ 2 | 1,315 | 1,190 | 592 | 592 | 49.75 | 111 | 0.67 | 8,3 | 8,8 | 11.70 | 102 | |
| 12/10 | 1,640 | 1,268 | 600 | 656 | 51.7 | 129 | 1.02 | 8,3 | 5,6 | 11.25 | 113 | |
| 12/17 | 1,524 | 1,272 | 579 | 681 | 53.5 | 120 | 0.73 | 8,2 | 7,0 | 11.00 | 116 | * Polk. |
| 12/17 | Diet: 200 gm. bread, 2 gm. salt mixture, 500 c.c. milk | | | | | | | | | | | |
| 12/24 | 1,445 | 1,214 | 595 | 607 | 50.0 | 119 | 0.66 | 9,0 | 5,0 | 11.00 | 110 | * Polk.+ |
| 12/30 | 1,375 | 1,115 | 556 | 546 | 48.9 | 122 | 0.75 | 8,2 | 5,4 | 10.75 | 104 | * Polk.+ |
| 1/6/20 | 1,141 | 1,120 | 611 | 499 | 44.5 | 102 | 0.76 | 6,7 | 5,2 | 11.00 | 102 | * Polk. |
| 1/21 | 940 | 1,075 | 636 | 439 | 40.8 | 87 | 0.62 | 6,9 | 5,8 | 10.80 | 100 | * Polk. |
| 1/23 | Diet: 250 gm. bread, 2 gm. salt mixture, 500 c.c. milk | | | | | | | | | | | |
| 2/10 | ..... | ..... | ... | ... | 42.0 | 102 | 0.68 | 7,5 | 8,6 | 11.30 | ... | * Polk. |
| 2/16 | 1,400 | 1,314 | 718 | 582 | 44.3 | 107 | 0.69 | 7,8 | 7,2 | 11.50 | 114 | * Polk. |

* Poikilocytosis of red blood cells.
† Salt mixture No. 185 (McCollum and Simmonds).

Table 89 is of much interest because we have control observations on the same dog. Fowler's solution has no effect whatsoever when given daily. The curve of hemoglobin regeneration shows a very slow rise from week to week, only approaching normal after five or six weeks. The normal level is never reached during the period of twelve weeks during which Fowler's solution is administered. A transfer to a period of larger food intake without Fowler's solution shows minor

fluctuations from week to week during a period of four months. It is unusual for a dog to tolerate this limited diet for this length of time without any symptoms of dietary deficiency disease.

TABLE 88.—BLOOD REGENERATION—SALT MIXTURE *

Dog 20-2. Bull mongrel. Male. Young adult

| Date, 1919 | Pigment Volume Hb. per Cent. Times Blood Volume | Blood Volume | Plasma Volume | R. B. C. Volume | R. B. C. Hematocrit | Hb. | Color Index | R. B. C., Million | W. B. C. | Weight | Blood per Kilogram | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C.c. | C.c. | C.c. | % | % | | | | Kg. | C.c. | |
| 10/27 | 1,878 | 1,498 | 758 | 732 | 48.9 | 125 | 0.79 | 7.9 | 7.0 | 17.25 | 87 | |
| 10/27 | Diet: Bread and milk | | | | | | | | | | | |
| 10/28 | Bled 375 c.c. | | | | | | | | | | | |
| 10/29 | Bled 375 c.c. No distress | | | | | | | | | | | |
| 10/31 | 866 | 1,111 | 760 | 334 | 30.1 | 78 | 0.98 | 4.2 | 21.6 | 16.35 | 68 | |
| 11/ 1 | Bled 278 c.c. | | | | | | | | | | | |
| 11/ 3 | 726 | 1,052 | 762 | 285 | 27.1 | 69 | 0.96 | 3.6 | 14.8 | 16.20 | 65 | |
| 11/ 3 | Diet: 200 gm. bread; 500 c.c. milk, 2 gm. salt mixture* | | | | | | | | | | | |
| 11/13 | 1,188 | 1,239 | 743 | 483 | 39.0 | 96 | 0.96 | 5.0 | 12.4 | 16.35 | 76 | |
| 11/20 | 1,430 | 1,400 | 788 | 566 | 42.6 | 102 | 0.80 | 6.4 | 12.2 | 15.75 | 89 | † Slight |
| 11/22 | Diet: 150 gm. bread, 500 c.c. milk, 2 gm. salt mixture* | | | | | | | | | | | |
| 11/26 | 1,285 | 1,377 | 795 | 574 | 41.7 | 98 | 0.66 | 7.0 | 6.0 | 15.50 | 89 | † Slight |
| 12/ 3 | 1,312 | 1,385 | 795 | 578 | 41.7 | 95 | 0.68 | 6.9 | 17.0 | 15.10 | 92 | † Slight |
| 12/10 | 1,502 | 1,386 | 757 | 616 | 44.4 | 108 | 0.80 | 6.8 | 11.4 | 14.95 | 93 | |
| 12/16 | 1,252 | 1,318 | 800 | 505 | 38.3 | 95 | 0.74 | 6.4 | 6.4 | 14.00 | 94 | † Polk.‡ |

* Salt mixture No. 185 (McCollum and Simmonds).
† Poikilocytosis of red blood cells.
‡ Distemper and dietary deficiency disease. Recovered.

Control observations on this same dog (Table 60[8]) show the favorable influence of a diet of cooked liver under similar conditions. Hemoglobin regeneration is complete within three weeks. This gives a striking example of the beneficial effect of certain diet factors as contrasted with certain drugs.

Table 90 shows the negative effect of Fowler's solution on the new hemoglobin regeneration. The drug is given over a period of twelve weeks. The first week shows a sharp rise which is common in such experiments. Thereafter little increase is noted from week to week. The pigment volume remains unchanged after the first three weeks. Compare other similar experiments on this same dog cited above, (Tables 85 and 88).

Following the long period of bread and milk diet, plus Fowler's solution, the dog was given a liberal mixed diet. As is not infrequent after long periods of limited diet, we note an actual fall in hemoglobin

8. Whipple, Robscheit and Hooper: Am. J. Physiol. **53**:251, 1920.

which in this case is due to the great gain in weight and increase in plasma volume. The following two weeks show continued gain in weight, increase in plasma volume, hemoglobin and red hematocrit. This illustrates the favorable reaction, even following a prolonged limited diet period, which follows a mixed diet rich in meat.

TABLE 89.—BLOOD REGENERATION—FOWLER'S SOLUTION

Dog 19-33. Bull mongrel. Male. Adult

| Date, 1920 | Pigment Volume = Hb. per Cent. Times Blood Volume | Blood Volume | Plasma Volume | R. B. C. Volume | R. B. C. Hematocrit | Hb. | Color Index | R. B. C., Millions | W. B. C. | Weight | Blood per Kilogram | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C.c. | C.c. | C.c. | % | % | | | | Kg. | C.c. | |
| 3/ 4 | 1,985 | 1,470 | 578 | 873 | 59.4 | 135 | 0.61 | 11.8 | 8,2 | 13.20 | 111 | |
| 3/ 4 | Diet: Bread and milk | | | | | | | | | | | |
| 3/ 5 | Bled 368 c.c. | | | | | | | | | | | |
| 3/ 6 | Bled 368 c.c. | | | | | | | | | | | |
| 3/ 8 | ..... | ..... | ... | ... | 34.0 | ... | .... | ... | .... | ..... | ... | |
| 3/ 8 | Bled 325 c.c. | | | | | | | | | | | |
| 3/10 | 780 | 1,207 | 860 | 345 | 28.6 | 64 | 0.77 | 4.2 | 14,2 | 12.75 | 95 | * Slight |
| 3/10 | Diet: 150 gm. bread, 500 c.c. milk, 5 drops Fowler's solution | | | | | | | | | | | |
| 3/17 | 1,114 | 1,475 | 944 | 516 | 35.0 | 76 | 0.73 | 5,2 | 12,4 | 12.75 | 116 | * Slight |
| 3/25 | 1,110 | 1,297 | 766 | 519 | 40.0 | 86 | 0.68 | 6,3 | 11,6 | 12.25 | 106 | * Slight |
| 4/ 1 | 1,409 | 1,505 | 828 | 662 | 44.0 | 94 | 0.65 | 7,2 | 10,4 | 12.00 | 125 | * Slight |
| 4/ 7 | 1,450 | 1,470 | 765 | 692 | 47.0 | 99 | 0.61 | 8,1 | 6,2 | 12.05 | 122 | * Slight |
| 4/15 | 1,455 | 1,470 | 771 | 685 | 46.6 | 101 | 0.63 | 7,9 | 6,4 | 11.95 | 123 | * Slight |
| 4/22 | 1,510 | 1,398 | 692 | 692 | 49.5 | 108 | 0.65 | 8,3 | 5,6 | 11.60 | 120 | * Slight |
| 4/29 | 1,506 | 1,468 | 745 | 708 | 48.2 | 102 | 0.59 | 8,7 | 4,8 | 11.55 | 127 | * Slight |
| 5/ 6 | 1,345 | 1,345 | 700 | 632 | 47.0 | 100 | 0.60 | 8,3 | 5,2 | 11.55 | 116 | * Polk.+ |
| 5/14 | 1,340 | 1,300 | 731 | 607 | 47.2 | 96 | 0.61 | 7,9 | 6,4 | 11.00 | 126 | * Polk.+ |
| 5/21 | 1,204 | 1,276 | 697 | 606 | 47.5 | 94 | 0.61 | 7,7 | 6,0 | 10.85 | 117 | * Slight |
| 5/28 | 1,419 | 1,375 | 702 | 667 | 48.5 | 103 | 0.61 | 8,5 | 5,2 | 10.70 | 128 | * Slight |
| 5/29 | Diet: 250 gm. bread, 500 c.c. milk. Fowler's solution discontinued | | | | | | | | | | | |
| 6/ 4 | ..... | ..... | ... | ... | 44.8 | 102 | .... | ... | .... | ..... | ... | |
| 6/11 | 1,305 | 1,393 | 743 | 587 | 43.7 | 95 | 0.57 | 8,2 | 6,4 | 11.70 | 114 | * Slight |
| 6/18 | 1,307 | 1,330 | 749 | 571 | 42.9 | 98 | 0.55 | 8,9 | 5,4 | 11.80 | 112 | * Polk. |
| 6/26 | 1,508 | 1,445 | 778 | 651 | 45.2 | 104 | 0.56 | 9,3 | 6,8 | 12.25 | 118 | * Polk. |
| 7/ 9 | 1,325 | 1,308 | 808 | 551 | 40.3 | 97 | 0.64 | 7,6 | 7,2 | 12.05 | 113 | * Polk. |
| 7/23 | 1,602 | 1,500 | 775 | 710 | 47.4 | 108 | 0.72 | 7,8 | 6,4 | 12.40 | 121 | * Slight |
| 8/18 | 1,960 | 1,621 | 803 | 808 | 49.5 | 121 | 0.79 | 7,6 | 6,0 | 12.85 | 126 | * Polk. |
| 8/30 | 1,705 | 1,505 | 790 | 711 | 47.2 | 113 | 0.74 | 7,6 | 5,8 | 12.10 | 124 | * Polk. |
| 9/ 9 | 1,630 | 1,538 | 854 | 669 | 43.5 | 106 | 0.68 | 7,8 | 6,2 | 12.60 | 122 | * Polk.+ |
| 9/22 | 1,550 | 1,550 | 894 | 640 | 41.3 | 100 | 0.69 | 7,2 | 7,2 | 12.75 | 121 | * Polk. |

* Poikilocytosis of red blood cells.

Table 91 shows that another arsenical, sodium cacodylate, is inert under these conditions. The curve of blood regeneration rises slowly and uniformly during 11 weeks but never returns to normal. This reaction is typical of many recorded for bread and milk alone. A change of diet gives a prompt increase in all hemoglobin figures and the normal level is reached in three weeks. Under such conditions this reaction to meat may not be as prompt, but it illustrates this favorable

reaction in contrast to the negative influence of this drug, sodium cacodylate.

TABLE 90.—Blood Regeneration—Fowler's Solution

Dog 20-2. Bull mongrel. Male. Young adult

| Date, 1920 | Pigment Volume = Hb. per Cent. Times Blood Volume | Blood Volume | Plasma Volume | R. B. C. Volume | R. B. C. Hematocrit | Hb. | Color Index | R. B. C., Million | W. B. C. | Weight | Blood per Kilogram | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C.c. | C.c. | C.c. | % | % | | | | Kg. | C.c. | |
| 3/ 4 | 2,282 | 1,915 | 882 | 1,013 | 52.9 | 119 | 0.60 | 10,0 | 13,4 | 17.65 | 108 | |
| 3/ 4 | Diet: Bread and milk | | | | | | | | | | | |
| 3/ 5 | Bled 480 c.c. | | | | | | | | | | | |
| 3/ 6 | Bled 480 c.c. | | | | | | | | | | | |
| 3/ 8 | ..... | ..... | ... | ... | 28.6 | ... | .... | ... | .... | ..... | ... | |
| 3/ 8 | Bled 350 c.c. | | | | | | | | | | | |
| 3/10 | 662 | 1,350 | 1,047 | 289 | 21.4 | 49 | 0.84 | 2,9 | 33,4 | 17.00 | 79 | |
| 3/10 | Diet: 150 gm. bread, 500 c.c. milk, 2 drops of Fowler's solution | | | | | | | | | | | |
| 3/17 | 1,180 | 1,370 | 803 | 554 | 40.5 | 86 | 0.81 | 5,3 | 7,0 | 15.85 | 86 | |
| 3/18 | Diet: 150 gm. bread, 500 c.c. milk, 5 drops of Fowler's solution | | | | | | | | | | | |
| 3/25 | 1,243 | 1,495 | 904 | 575 | 38.5 | 88 | 0.78 | 5,3 | 6,8 | 15.60 | 96 | |
| 4/ 1 | 1,410 | 1,535 | 857 | 695 | 45.3 | 92 | 0.71 | 6,5 | 7,2 | 15.00 | 102 | |
| 4/ 7 | 1,660 | 1,680 | 885 | 786 | 46.8 | 99 | 0.73 | 6,8 | 5,4 | 15.05 | 112 | |
| 4/15 | 1,750 | 1,730 | 912 | 815 | 47.1 | 101 | 0.73 | 6,9 | 5,6 | 15.05 | 115 | |
| 4/22 | 1,715 | 1,715 | 850 | 850 | 49.5 | 100 | 0.60 | 8,4 | 6,6 | 14.85 | 115 | |
| 4/29 | 1,695 | 1,740 | 916 | 808 | 46.4 | 97 | 0.65 | 7,5 | 7,0 | 14.65 | 119 | * Slight |
| 5/ 6 | 1,530 | 1,570 | 820 | 734 | 46.8 | 98 | 0.60 | 8,1 | 6,8 | 14.55 | 108 | * Polk.+ |
| 5/14 | 1,565 | 1,565 | 820 | 738 | 47.1 | 100 | 0.63 | 8,0 | 5,8 | 13.75 | 114 | * Polk.+ |
| 5/21 | 1,387 | 1,547 | 867 | 675 | 43.6 | 90 | 0.62 | 7,2 | 6,4 | 13.50 | 115 | * Polk. |
| 5/28 | 1,554 | 1,568 | 828 | 719 | 46.0 | 99 | 0.70 | 7,1 | 6,8 | 13.45 | 116 | * Slight |
| 5/28 | Diet: 100 gm. bread, 300 gm. meat scraps, 500 c.c. milk. Fowler's solution discontinued | | | | | | | | | | | |
| 6/ 4 | ..... | ..... | ... | ... | 43.9 | 99 | .... | ... | .... | ..... | ... | |
| 6/11 | 1,395 | 1,545 | 875 | 680 | 44.0 | 90 | 0.57 | 7,9 | 6,6 | 15.75 | 98 | * Polk. |
| 6/11 | Diet: 100 gm. bread, 450 gm. meat scraps, 500 c.c. milk | | | | | | | | | | | |
| 6/18 | 2,148 | 1,865 | 924 | 924 | 49.5 | 115 | 0.66 | 8,4 | 10,0 | 16.40 | 114 | |
| 6/25 | 2,008 | 1,820 | 920 | 884 | 48.5 | 110 | 0.69 | 8,0 | 8,8 | 17.25 | 106 | |

* Poikilocytosis of red blood cells.

Table 92 confirms the reaction noted in the preceding Table 91. We believe there is not a bit of evidence that the sodium cacodylate has any effect upon this reaction. There is every reason to believe that an identical reaction would have been observed in this experiment had the drug not been given. Compare Table 86 above, in which a more favorable reaction is associated with the oral administration of a standard salt mixture (McCollum and Simmonds).

## SUMMARY

Iron in the form of Blaud's pills is inert when given under controlled conditions in anemia periods under the conditions of these experiments (Paper V of this series [4]).

The anemia is produced by hemorrhage, and the curve of regeneration followed week by week, the dogs being maintained on a fixed diet.

Iron in the form of ferric citrate (subcutaneously) and ovoferrin (orally) has no significant effect on the curve of hemoglobin regeneration under controlled conditions.

TABLE 91.—BLOOD REGENERATION—SODIUM CACODYLATE

Dog 20-5. Bull mongrel. Male. Young adult

| Date, 1920 | Pigment Volume = Hb. per Cent. Times Blood Volume | Blood Volume | Plasma Volume | R. B. C. Volume | R. B. C. Hematocrit | Hb. | Color Index | R. B. C., Million | W. B. C. | Weight | Blood per Kilogram | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C.c. | C.c. | C.c. | % | % | | | | Kg. | C.c. | |
| 3/ 4 | 2,360 | 1,800 | 774 | 1,008 | 56.0 | 131 | 0.75 | 8.7 | 12,2 | 13.75 | 131 | |
| 3/ 4 | Diet: Bread and milk | | | | | | | | | | | |
| 3/ 5 | Bled 450 c.c. | | | | | | | | | | | |
| 3/ 6 | Bled 450 c.c. | | | | | | | | | | | |
| 3/ 8 | ..... | ..... | ... | ... | 27.5 | ... | .... | ... | .... | ..... | ... | |
| 3/ 8 | Bled 300 c.c. | | | | | | | | | | | |
| 3/10 | 530 | 1,170 | 924 | 234 | 20.0 | 44 | 0.77 | 2,9 | 13,6 | 13.40 | 87 | |
| 3/10 | Diet: 150 gm. bread, 500 c.c. milk, 0.1 gm. sodium cacodylate subcutaneously | | | | | | | | | | | |
| 3/17 | 637 | 1,250 | 946 | 310 | 24.8 | 51 | 0.77 | 3,3 | 12,6 | 13.25 | 94 | |
| 3/25 | 798 | 1,319 | 927 | 369 | 28.2 | 61 | 0.65 | 4,7 | 11,8 | 13.00 | 101 | Slight |
| 4/ 1 | 782 | 1,325 | 922 | 392 | 29.6 | 59 | 0.54 | 5,5 | 11,2 | 12.90 | 103 | * Poik.+ |
| 4/ 7 | 1,059 | 1,370 | 872 | 512 | 37.3 | 79 | 0.50 | 7,8 | 8,8 | 12.85 | 107 | * Poik. |
| 4/15 | 970 | 1,320 | 857 | 448 | 34.0 | 73 | 0.52 | 7,1 | 8,4 | 12.85 | 103 | * Poik.++ |
| 4/22 | 1,102 | 1,352 | 806 | 542 | 40.1 | 86 | 0.45 | 9,6 | 7,6 | 12.45 | 108 | * Poik.++ |
| 4/29 | 1,125 | 1,380 | 823 | 548 | 39.7 | 81 | 0.60 | 7,6 | 8,8 | 12.55 | 110 | * Poik. |
| 5/ 6 | 1,258 | 1,455 | 840 | 600 | 41.2 | 86 | 0.49 | 8,9 | 8,2 | 12.40 | 117 | * Poik.++ |
| 5/14 | 1,262 | 1,360 | 754 | 592 | 43.6 | 92 | 0.58 | 8,0 | 6,0 | 12.25 | 111 | * Poik.+ |
| 5/21 | 1,225 | 1,385 | 788 | 584 | 42.2 | 88 | 0.50 | 8,9 | 6,2 | 12.40 | 112 | * Poik.++ |
| 5/28 | 1,330 | 1,420 | 778 | 664 | 44.7 | 94 | 0.73 | 9,4 | 5,0 | 12.25 | 116 | * Poik.+ |
| 5/28 | Diet: 100 gm. bread, 300 gm. meat scraps; 500 c.c. milk. Sod. cacodylate discontinued | | | | | | | | | | | |
| 6/ 4 | ..... | ..... | ... | ... | 45.0 | 100 | .... | ... | .... | ..... | ... | |
| 6/11 | 1,745 | 1,650 | 868 | 768 | 46.5 | 106 | 0.58 | 9,1 | 6,0 | 14.10 | 117 | * Poik. |
| 6/11 | Diet: 100 gm. bread, 450 gm. meat scraps, 500 c.c. milk | | | | | | | | | | | |
| 6/18 | 1,998 | 1,745 | 876 | 892 | 48.8 | 114 | 0.58 | 9,8 | 17,4 | 14.90 | 117 | |
| 6/25 | 2,325 | 1,861 | 850 | 996 | 53.5 | 125 | 0.63 | 10,5 | 16,4 | 15.50 | 120 | |

* Poikilocytosis of red blood cells.

Iron forming a part of a standard salt mixture (McCollum and Simmonds) may be concerned in a somewhat favorable anemia reaction, but even this reaction is not surely related to the iron salt. At best this reaction does not compare favorably with those recorded in association with certain potent diet factors.

Iron in the form of hemoglobin (organic iron) may be concerned in the somewhat favorable reaction observed following the administration of hemoglobin orally, intraperitoneally or intravenously. But the iron may be less concerned in this reaction than the pyrrol complex (Paper V of this series [4]).

Arsenic in the form of sodium cacodylate or Fowler's solution is inert in these same anemia periods. No drug has been tested which can compare with the meat factors in stimulating a rapid regeneration of hemoglobin during these anemia periods induced by simple hemorrhage.

TABLE 92.—BLOOD REGENERATION—SODIUM CACODYLATE

Dog 20-3. Bull mongrel. Male. Young adult

| Date, 1920 | Pigment Volume = Hb. per Cent. Times Blood Volume | Blood Volume | Plasma Volume | R. B. C. Volume | R. B. C. Hematocrit | Hb. | Color Index | R. B. C., Million | W. B. C. | Weight | Blood per Kilogram | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C.c. | C.c. | C.c. | % | % | | | | Kg. | C.c. | |
| 3/ 4 | 2,166 | 1,865 | 838 | 1,010 | 54.2 | 116 | 0.69 | 8.4 | 13.2 | 16.95 | 110 | |
| 3/ 4 | Diet: Bread and milk | | | | | | | | | | | |
| 3/ 5 | Bled 467 c.c. | | | | | | | | | | | |
| 3/ 6 | Bled 467 c.c. | | | | | | | | | | | |
| 3/ 8 | ..... | ..... | ... | ... | 24.4 | ... | .... | ... | .... | ..... | ... | |
| 3/ 8 | Bled 200 c.c. | | | | | | | | | | | |
| 3/10 | 640 | 1,320 | 1,009 | 294 | 22.3 | 49 | 0.93 | 2,6 | 30,8 | 16.40 | 80 | |
| 3/10 | Diet: 150 gm. bread, 500 c.c. milk, 0.1 gm. sodium cacodylate subcutaneously | | | | | | | | | | | |
| 3/17 | 1,150 | 1,548 | 1,018 | 508 | 32.8 | 70 | 0.81 | 4,3 | 10,6 | 16.05 | 96 | |
| 3/25 | 1,297 | 1,563 | 923 | 633 | 40.5 | 83 | 0.78 | 5,8 | 9,4 | 15.00 | 104 | * Slight |
| 4/ 1 | 1,480 | 1,625 | 896 | 745 | 45.8 | 91 | 0.72 | 6,3 | 9,6 | 15.00 | 108 | * Slight |
| 4/ 7 | 1,580 | 1,602 | 850 | 736 | 45.3 | 99 | 0.81 | 6,1 | 8,2 | 14.85 | 108 | * Slight |
| 4/15 | 1,755 | 1,675 | 874 | 796 | 47.5 | 105 | 0.81 | 6,5 | 7,8 | 14.20 | 118 | * Slight |
| 4/22 | 1,775 | 1,715 | 864 | 840 | 49.0 | 103 | 0.71 | 7,3 | 5,6 | 14.25 | 120 | * Slight |
| 4/29 | 1,788 | 1,700 | 808 | 876 | 51.5 | 105 | 0.65 | 8,1 | 6,8 | 13.95 | 122 | * Slight |
| 5/ 6 | 1,815 | 1,760 | 904 | 834 | 47.4 | 103 | 0.72 | 7,2 | 6,4 | 13.80 | 127 | * Polk. |
| 5/14 | 1,600 | 1,497 | 752 | 732 | 48.9 | 113 | 0.86 | 6,6 | 10,6 | 13.35 | 112 | * Slight |
| 5/21 | 1,317 | 1,480 | 829 | 636 | 43.0 | 89 | 0.74 | 6,0 | 9,4 | 13.05 | 113 | * Polk. |
| 5/28 | 1,310 | 1,455 | 837 | 612 | 42.0 | 90 | 0.76 | 5,9 | 8,4 | 12.55 | 116 | * Slight |
| 5/29 | Diet: 100 gm. bread, 300 gm. meat scraps, 500 c.c. milk. No sodium cacodylate | | | | | | | | | | | |
| 6/ 4 | ..... | ..... | ... | ... | 43.6 | 101 | .... | ... | .... | ..... | ... | |
| 6/11 | 1,607 | 1,630 | 848 | 765 | 47.0 | 99 | 0.70 | 7,0 | 7,2 | 14.20 | 114 | |
| 6/11 | Diet: 100 gm. bread, 450 gm. meat scraps, 500 c.c. milk | | | | | | | | | | | |
| 6/18 | 1,852 | 1,657 | 826 | 816 | 49.2 | 112 | 0.67 | 8,4 | 12,4 | 14.65 | 113 | |
| 6/25 | 1,782 | 1,647 | 851 | 784 | 47.6 | 108 | 0.68 | 7,9 | 10,6 | 15.75 | 105 | |

* Poikilocytosis of red blood cells.

These carefully controlled experiments give no support to the time honored custom of administering iron and certain other drugs in conditions of simple anemia. The burden of proof now rests with those who claim that any given drug is potent under such conditions. In such experiments or clinical observations the diet factors must be carefully studied. We believe it will be of much clinical importance to record accurate observations in human cases, giving particular attention to a variety of diet factors.

9. McCollum and Simmonds: J. Biol. Chem. **33**:63, 1918.

# THE CREATININ COEFFICIENT IN PULMONARY TUBERCULOSIS *

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In the light of the significant rôle of creatinin excretion in endogenous metabolism, it was deemed that it might prove of some interest to determine the creatinin coefficient in a series of graded, clinically uncomplicated, cases of pulmonary tuberculosis, particularly as there are operative, in this condition, two somewhat opposing factors of undoubted metabolic importance, namely continued pyrexia and progressive wasting of muscle mass.

But few cases of pulmonary tuberculosis have been reported in the literature from this point of view, and these show findings both indeterminate and in poor accord. Thus Hofmann,[1] employing a now obsolete procedure of creatinin determination and making no provision as to diet control, reports one advanced, though apparently afebrile case (patient aged 34), in which there was noted a slight decrease of creatinin output—0.496 gm. per twenty-four hours as opposed to his normal value of 0.687 gm. Van Hoogenhyze and Verploegh,[2] on the basis of Folin's technic, and utilizing a low protein diet, report a febrile case (patient aged 72) marked by slight decrease in creatinin excretion —1.05 gm. (average) per twenty-four hours. McClure,[3] also utilizing Folin's technic and employing a modified (purin and nuclein free) Shaffer-Coleman [4] diet, reports four febrile cases. The first case (patient aged 19), in which there was a positive Wassermann reaction, showed irregular increase with wide range (from 0.606 to 2.052 gm. per twenty-four hours). In the second case (patient aged 27), complicated by hemopneumothorax, there was likewise noted occasional increase in creatinin output with a range of from 0.624 to 1.956 gm. per twenty-four hours. In the third case, one of tuberculous bronchopneumonia (patient aged 28), there was observed practically no increase and a range of from 0.607 to 1.291 gm. per twenty-four hours, while, in the last case (patient aged 25), also one of tuberculous bronchopneumonia, there was found a slight decrease, with a range of from 0.540 to 1.000 gm. per twenty-four hours.

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* From the laboratory of the Sea View Hospital.

1. Hofmann, K. B.: Virchows Arch. f. path. Anat. **48**:358, 1869.
2. Van Hoogenhyze, C. J. C., and Verploegh, H.: Ztschr. f. Physiol. Chem **57**:162, 1908.
3. McClure, C. W.: Arch. Int. Med. **22**:719 (Dec.) 1918.
4. Shaffer, P. A., and Coleman, W.: Arch. Int. Med **4**:538 (Nov.) 190

In regard to the normal rate of creatinin excretion, it has been determined by Shaffer [5] that the creatinin coefficient (milligrams of creatinin-nitrogen excreted per kilogram of body weight in twenty-four hours) represents a practical constant in ordinary individuals, the average figure being 8.1. Values under 7, he found, are distinctly abnormal, except in aged, poorly developed, or obese subjects. This constant seems to be the most convenient and generally accepted medium for the expression of creatinin values.

## PROCEDURE

Three groups of five cases of pulmonary tuberculosis, uncomplicated as far as could be determined clinically, were selected in accordance with Rathbun's [6] classification, as representing three progressive grades of disease activity. Organically, these cases were all of his "moderately advanced" or "far advanced" (third group) types (q. v.), falling functionally or symptomatically, however, into the three groups of his classification, as follows: A, afebrile, absence of constitutional disturbance, ambulant and doing light work; B, slightly febrile, slight constitutional disturbance, in bed one-half day; C, definitely febrile, marked constitutional disturbance, confined to bed entire day and general condition serious to critical. The cases were all males and care was taken to select no patients showing evidence of obesity and to exclude adolescent and senile types.

The subjects were placed on a strictly meat free diet, and after a preliminary period of forty-eight hours, creatinin determinations were made on three successive days from preserved twenty-four-hour urine samples. These determinations were made according to Folin's method, as outlined by Hawk,[7] utilizing the Duboscq colorimeter and a potassium bichromate standard, the average of triplicate readings being taken in each case. Calculations were made on the basis of milligrams of creatinin-nitrogen per kilogram of body weight excreted per twenty-four hours (Shaffer's creatinin coefficient) and the results tabulated as shown in the accompanying table.

## COMMENT

It will be seen that the findings have been, for the most part, of consistent uniformity, with most variation in group A, and that, in all three groups, the average values have been definitely below the normal constant (8.1), as determined by Shaffer. On the other hand, there seems to be but little difference between the three grades, as compared

5. Shaffer, P.: Am. J. Physiol. **23**:1, 1908.
6. Rathbun, W. L.: Tuberculosis, Monograph, Dept. Health, New York City No. 4, March, 1917.
7. Hawk, P. B.: Physiologic Chemistry, Philadelphia, Ed. 6, 1918.

## Creatinin Coefficient of Five Subjects on a Meat-Free Diet

| Case | Grade | Date | Creatinin Coefficient | Body Weight, Kg. | Age | Case | Grade | Date | Creatinin Coefficient | Body Weight, Kg. | Age | Case | Grade | Date | Creatinin Coefficient | Body Weight, Kg. | Age |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1-Ra. | A | 7/30/20 | 6.07 | 66.1 | 29 | 6-P. | B | 8/3/20 | 7.14 | 48.7 | 30 | 11-Re. | C | 7/28/20 | 6.88 | 52.7 | 30 |
| | | 7/31/20 | 5.38 | | | | | 8/4/20 | 8.22 | | | | | 7/29/20 | 6.37 | | |
| | | 8/ 1/20 | 4.86 | | | | | 8/5/20 | 6.34 | | | | | 7/30/20 | 7.59 | | |
| | | Average | 5.44 | | | | | Average | 7.26 | | | | | Average | 6.94 | | |
| 2-Wy. | A | 7/30/20 | .... | 74.0 | 36 | 7-W.W. | B | 8/3/20 | 7.05 | 48.9 | 54 | 12-M. | C | 7/28/20 | 5.53 | 51.3 | 34 |
| | | 7/31/20 | 7.56 | | | | | 8/4/20 | 6.56 | | | | | 7/29/20 | 5.58 | | |
| | | 8/ 1/20 | 5.34 | | | | | 8/5/20 | 7.68 | | | | | 7/30/20 | .... | | |
| | | Average | 6.46 | | | | | Average | 7.09 | | | | | Average | 5.55 | | |
| 3-D. | A | 7/30/20 | 7.04 | 66.3 | 61 | 8-Ko. | B | 8/3/20 | 6.05 | 57.7 | 36 | 13-B. | C | 7/28/20 | 3.82 | 56.8 | 28 |
| | | 7/31/20 | .... | | | | | 8/4/20 | 6.26 | | | | | 7/29/20 | 4.07 | | |
| | | 8/ 1/20 | .... | | | | | 8/5/20 | 6.37 | | | | | 7/30/20 | 5.56 | | |
| | | Average | 7.04 | | | | | Average | 6.22 | | | | | Average | 4.48 | | |
| 4-H. | A | 7/30/20 | 5.55 | 71.3 | 30 | 9-By. | B | 8/3/20 | 5.36 | 52.2 | 24 | 14-G. | C | 7/28/20 | 6.18 | 46.3 | 30 |
| | | 7/31/20 | 4.93 | | | | | 8/4/20 | 7.29 | | | | | 7/29/20 | 5.82 | | |
| | | 8/ 1/20 | 4.16 | | | | | 8/5/20 | .... | | | | | 7/30/20 | 6.27 | | |
| | | Average | 4.88 | | | | | Average | 6.33 | | | | | Average | 6.09 | | |
| 5-Kr. | A | 10/14/20 | 3.06 | 64.5 | 31 | 10-T.W. | B | 8/3/20 | 7.24 | 62.7 | 40 | 15-L. | C | 7/28/20 | .... | 50.3 | 29 |
| | | 10/15/20 | 3.58 | | | | | 8/4/20 | 7.04 | | | | | 7/29/20 | 5.38 | | |
| | | 10/16/20 | 4.47 | | | | | 8/5/20 | 7.11 | | | | | 7/30/20 | 6.91 | | |
| | | Average | 3.70 | | | | | Average | 7.13 | | | | | Average | 6.14 | | |
| General average..... | | | 5.50 | 68.4 | | General average..... | | | 6.80 | 54.0 | | General average..... | | | 5.84 | 51.4 | |

with one another, save that the B cases appear, on the whole, to show a slightly higher coefficient than either A or C. This might possibly be accounted for on the basis of the increased catabolism, due to fever and increased disease activity, not present in A, and not offset, as in C, by extreme wasting and general debility and asthenia. It would seem therefore, that in pulmonary tuberculosis, creatinin excretion increases with increase in disease activity, up to a certain point, at which a decrease becomes manifest dependent, probably, on progressive tissue wasting and generally lowered plane of vital activity.

These findings bear out, in a general way, the tendency indicated in the work of Hofmann and Van Hoogenhyze and Verploegh and, also, may serve to throw some light on the apparent disagreement between their findings and those of McClure.

It is of interest to note, in this connection, that McCann and Barr,[8] working with tuberculous patients from the point of view of calorimetric investigation, have recently found that due to weight-loss compensating for increase in metabolism dependent on disease activity, the basal heat production, in this disease, may represent a value definitely below that obtaining in health for the same individual.

## SUMMARY

On the basis of the data secured in this study, it seems that, in apparently clinically uncomplicated cases of pulmonary tuberculosis, the creatinin coefficient is slightly below the average normal figure, and that it reaches its greatest height in middle grade cases, i.e., those in which increased catabolism, due to disease activity, has not yet been offset by excessive tissue waste and generally lowered vitality.

8. McCann, W. S., and Barr, D. P.: Arch. Int. Med. **26**:663 (Dec.) 1920.

# REMARKS ON STANDARDS FOR NORMAL BASAL METABOLISM.*

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Indirect calorimetry, as a result of the pioneer work of DuBois and his colaborators,[1] has become generally adopted in the last two or three years, in this country at least, as a routine method of laboratory diagnosis in certain diseases, especially in those of the ductless glands. As a functional test of the thyroid gland, the level of the basal metabolism is being determined at the present time in many clinics.

Clinicians, of course, wish to use the most accurate criteria available in judging of the normality or abnormality of the basal metabolism of their patients, and yet at present they may well be puzzled in choosing between the several methods that have been proposed for the purpose by various investigators. It is with the hope of throwing light on this phase of the subject that the present communication is made.

## METHODS FOR PREDICTING THE BASAL METABOLISM OF NORMAL PERSONS

*Body Surface Law.*—The search for suitable criteria has centered chiefly about the so-called body surface law of Rubner. The principle embodied in this law, which is that the basal metabolism is a simple function of the body surface, has been disputed by Benedict,[2] and quite lately by Dreyer,[3] and as Boothby and Sandiford [4] have recently pointed out, such objections, in a strict sense, are valid. Nevertheless, in a broader sense Rubner's Law has never been disproved, and while it may be true that the basal metabolism is not strictly proportional to, nor, perhaps, determined by, surface area, the fact remains that it is more nearly proportional to area than to any other one factor so far discovered. Pertinent in this connection are the studies by Means,[5] of obesity,[6] which showed that even in very marked grades of obesity, there was no fundamental deviation from normal in basal metabolism

* From the Medical Service of the Massachusetts General Hospital, aided in part by a gift from Dr. William Norton Bullard.

1. Du Bois, E. F., et al.: Series of papers on Clinical Calorimetry beginning, Arch. Int. Med. **15**:793 (July) 1915.
2. Benedict, F. G.: Boston M. & S. J. **182**:243, 1915.
3. Dreyer, G.: Lancet **1**:289, 1920.
4. Boothby, W. M., and Sandiford, I.: Basal Metabolic Rate Determinations, Philadelphia, W. B. Saunders Co., 1920.
5. Means, J. H.: Proc. Soc. Exper. Biol. & Med. **12**:13, 1914; J. M. Research **32**:121, 1915; Arch. Int. Med. **17**:704 (July) 1916.
6. The data on these cases of obesity together with that on one new one is given in Table 2 of the present paper.

expressed in terms of surface area, whereas there was a marked reduction (30 per cent. or more) when it was expressed in terms of body weight.

The history of the body surface law is very completely covered in the recent monograph of Harris and Benedict.[7] The difficulty which has confronted investigators since the time when the relationship between metabolism and area was first appreciated has lain chiefly in the lack of an accurate method for measuring or calculating body surface area from the body weight, such for example as those of Meeh,[8] and of Lissauer.[9] For persons of normal build they may serve very well, but for those who vary from the normal, they may serve badly. Of two persons of the same weight, one being short and stout, the other tall and thin, the latter would have the greater actual area, yet by Meeh's or similar formulas the calculated area would be the same.

*Du Bois Linear Formula.*—It was to overcome just such faults in formulas of the Meeh type that the Du Bois formulas were devised. By the first of these, the so-called linear formula,[10] which was first published in 1914, the body surface is calculated from about nineteen measurements of the body. The principle is to divide the body into parts and calculate the area of each part from its length multiplied by its average circumference and by a constant. The sum of the parts gives the total body surface area. The constants for the several parts were derived from the areas of the parts as determined by actual casts. Casts were made of the bodies of ten individuals of widely different shapes.[11] It was found that the area as calculated by the linear formula varied on an average less than 1.7 per cent. from the areas as actually measured from the casts. It was with the advent of this formula that calorimetry became available to the clinician.[12] In the linear formula, the clinical investigator is equipped with a method that will give him accurately the surface area of individuals of any shape.

*Du Bois Height Weight Formula and Chart.*—In 1916, the Du Boises [14] brought out a still simpler formula, the so-called height-weight

7. Harris, J. A., and Benedict, F. G.: Carnegie Institution of Washington, Publication No. 279, 1919.

8. Meeh: Ztschr. f. Biol. **15**:425, 1879.

9. Lissauer: Jahrb. f. Kinderh., N. F. **58**:392, 1903.

10. Du Bois, D., and Du Bois, E. F.: Proc. Soc. Exper. Biol. & Med. **12**: 16, 1914. Ibid., Arch. Int. Med. **15**:868 (July) 1915.

11. The cast of one of these, Mrs. McK. (Table 2), was made at the Massachusetts General Hospital.

12. In addition to the obesity data given in Table 2, attention is called to a previous paper by one of us (J. H. M.[13]), in which it was shown that even in normal persons there was less variation in the metabolism by the linear formula, than by that of Meeh.

13. Means, J. H.: J. Biol. Chem. **21**:263, 1915.

14. Du Bois, D., and Du Bois, E. F.: Arch. Int. Med. **17**:863 (July) 1916.

formula. This was worked out from the results obtained in a large series of persons by the linear formula, and enables one to obtain the surface area directly from the height and weight.[15]

The height-weight formula, which has been still further simplified into the height-weight chart, is the method in use in most clinics today. At the Massachusetts General Hospital the determination of the basal metabolism in disease was begun early in 1914, from then until the fall of 1915 the linear formula was used; since then the height-weight chart has been used, except that in very stout persons we still use the linear. In this clinic as in other clinics the calories per square meter per hour are compared with the Sage Institute normal standards. These standards have been changed slightly from time to time; the most recent ones will be found in the paper of Aub and Du Bois[16] published in 1917.

*Harris-Benedict Prediction Tables.*—As has been said, clinical calorimetry has become part of the diagnostic armamentarium of many clinics. It is, therefore, obviously desirable that in so far as possible uniform standards be employed. As has been indicated, the Du Bois height-weight chart with the Sage Institute standards is the method in common use today. However, since no lesser authorities than Benedict[7] in this country and Dreyer[3] in England have each recently proposed new methods for predicting normal metabolism, the clinical calorimetrist may well be in doubt as to which of these, the Du Bois, the Harris-Benedict, or the Dreyer, he should use.

TABLE 1.—Comparison of Prediction Methods. Data on Normal Persons

| | Average Deviation Without Regard to Sign, per Cent. | | | Average Deviation With Regard to Sign, per Cent. | | |
|---|---|---|---|---|---|---|
| | Du Bois Height-Weight Formula | Dreyer | Harris-Benedict | Du Bois Height-Weight Formula | Dreyer | Harris-Benedict |
| Series of 8 normal men Means[13] | 6.21* | 3.70 | 4.40 | —6.21* | —2.12 | —4.40 |
| Series of 31 normal men Carpenter et al[7] | 5.10* | 5.94 | 5.30 | —1.69* | +0.10 | +0.46 |

* Our calculations; other figures are from Dreyer's paper.[3]

The Harris-Benedict method takes the form of a series of tables in which are given prediction figures of what the metabolism should be in a normal adult of either sex and of any height, weight or age. The figures were developed from the data of observations made on 103 women and 136 men at the Carnegie Nutrition Laboratory in Boston.

15. For the mathematical expression one is referred to the original paper.
16. Aub, J. C., and Du Bois, E. F.: Arch. Int. Med. **19**:823 (July) 1917.

*The Dreyer Formulas.*—The Dreyer formulas are several. They take into consideration one less factor than either the Du Bois or the Harris-Benedict. The last two take into consideration height, weight, age and sex. The Dreyer formulas are based on age, sex, and one other factor, either weight, trunk length or circumference of thorax. Dreyer derived his constants from the Harris-Benedict data.

*Comparison of the Du Bois, Harris-Benedict and Dreyer Methods.*—The immediate object of this paper is to scrutinize these three methods, the Du Bois height-weight formula or chart used in conjunction with the Sage standards, the Harris-Benedict prediction tables, and the Dreyer weight formula. An attempt will be made to learn their respective merits and limitations, their similarities and dissimilarities.

We have several ways of making such a scrutiny. In the first place, we can see which method actually predicts with the least error the metabolism of healthy persons of normal build. Next, we can do the same with persons with abnormally shaped bodies, obese subjects for example. Lastly, we can compare the deviations from normal by the several methods (one with another) in patients whose metabolism is known to be abnormal.

*In Normal Persons.*—There are shown in Table 1 the average variations by these methods of a series of eight normal men studied by Means [18] and of a series of thirty-one studied by Carpenter and collaborators.[7] The results obtained in both these series by the Harris-Benedict method have been discussed by Harris and Benedict,[7] and those obtained by both Harris-Benedict and Dreyer methods have been discussed by Dreyer.[3]

In analyzing such a series of results, we have two modes of attack. We can compare the average deviations from different standards or predictions, regardless of whether they are too high or too low, that is to say, without regard to sign, or we can cancel the positive deviations against the negative and find the average deviation with regard to sign. The former way gives the truest idea of the success in metabolism prediction of the method under consideration, for the lower the average deviation without regard to sign the closer has the predicted come to the observed in the majority of instances. This is particularly true if in addition to the average, we know the maximum deviation of the series.

The average deviation with regard to sign, that is to say, when plus deviations neutralize minus ones of the same magnitude, tells us chiefly whether the series has a positive or negative bias or trend, but we must regard not only this average but at the same time the distribution of its individual components about it, the probability curve

in other words, lest we be led astray by the cancellation of several small plus deviations by a single large minus one, or vice versa.

A case in point is the characterization by Harris and Benedict as of an anomalous nature the Means series of eight normal men as well as the series of ten normal men of Magnus-Levy and Falk.[17] The interpretation here is dependent upon the significance given to averages. All of the members of the Means series deviate below the predicted metabolism level while seven out of ten of the Magnus-Levy and Falk series deviate above it. This, we are prepared to admit, may mean that the former series is composed of very slightly subnormal individuals and the latter of very slightly supernormal ones. We cannot, however, agree with Harris and Benedict that the members of either of these series are more abnormal than are those of the Carpenter series merely because in the Carpenter series the positive deviations counterbalance the negative. There are five individuals in the Carpenter series, or nearly one-sixth of the whole, all of whom are more abnormal than are any of those in the Means series. The fact that some are supernormal and some subnormal does not increase the normality of the series as a whole. The average deviation without regard to sign is the true index of the normality or lack of normality of a series. That factor is less (4.40 per cent.) in the case of the Means series than in that of the Carpenter series (5.30 per cent.). We cannot, therefore, agree that either the Means series or the Magnus-Levy and Falk series are anomalous, or that they are unfit for combination with other series for purposes of generalization. The low average deviation in the Means series shows a high grade of normality in that series. The fact that the deviations, though slight, were all in the direction of subnormality may be explained by the fact that this series was entirely composed of subjects of a non-athletic type, whereas the prediction figures were based on subjects of all types.

With these remarks as to the significance or lack of significance of averages, let us now turn to Table 1 and note the results obtained by the three different formulas. In the case of the Means series the lowest average deviation was obtained with the Dreyer formula, in that of the Carpenter series it was with the Du Bois formula. In both series the lowest deviation with regard to sign was with the Dreyer formula. That is to say, with the last named there is the least tendency toward a positive or negative trend. The greatest average deviations were with the Du Bois formula in the case of the Means series, and with the Dreyer in the case of the Carpenter series. In other words, as applied to two series of normal men the three methods give deviations of about the same order of magnitude.

17. Magnus-Levy, A., and Falk: Arch. f. Anat. u. Physiol. Suppl., 1899, p. 314.

*In Obese Persons.*—Let us now apply these formulas to persons of abnormal build. In Table 2 are given the data on the five cases of obesity previously published by Means [5] together with those of one new case, Mrs. F. When originally published, the metabolism of these patients was calculated in terms of the linear formula only. We have now added the height-weight, Harris-Benedict and Dreyer data. The conclusion was drawn originally that there was no fundamental change in the metabolism in obesity. As will be seen in Table 2, the results obtained with the other methods are in general similar to those obtained with the linear formula. The closest prediction is that of the Harris-Benedict method, the average deviation being only 3.3 per cent., the linear comes next with 4.9 per cent., then the height-weight formula with 5.6 per cent., and lastly, the Dreyer with 6.5 per cent. Taking signs into consideration, we find a plus bias for the series with the height-weight and Dreyer formulas and a negative one with the Harris-Benedict and linear. The maximum deviation for all six subjects by all four methods is only + 11.5 per cent. in the case of Mrs. B. by the height-weight formula. By the linear she is — 1.7 per cent., and by the Harris-Benedict + 1.7 per cent. and by the Dreyer + 10.5 per cent. Mrs. McK. is slightly subnormal by all methods, Mrs. McI. is slightly supernormal by all methods, and the rest show deviations above by some and below by other of the methods. Taken as a whole, we believe these figures constitute strong confirmation of the conclusion originally drawn from the linear results alone, namely, that there is no fundamental change in the level of the basal metabolism in simple obesity. They all show that in obesity the Harris-Benedict method gives a slightly closer prediction than the Du Bois formulas, and they closer than the Dreyer. The last is not surprising since the latter method takes no account of height. In fact, the extraordinary thing is that the Dreyer prediction is as good as it is.

*In Persons with Abnormal Metabolism.*—So much for the relative merits of these three methods of prediction in the case of persons who may be expected a priori to have normal metabolism. Let us now apply them to persons who may be expected to have abnormal metabolism. The problem here is a slightly different one. It is not so much a question of finding the method which in the case of abnormal metabolism gives the least deviation from normal, as it is of comparing the general trend of the deviation by one method, with that by another, to see, in other words, whether in a series of patients with varying elevations or depressions of metabolism the deviations by one method run parallel with those by another, or whether there is any constant tendency for one method to give greater deviations than another.

To accomplish this purpose, we have prepared three figures in which we have plotted the deviations shown by a series of 160 hospital patients.

We used the graphic method in this instance, believing that it would more simply demonstrate the facts than would tables of numbers. The patients, data on whom constitute the series, were selected only with a view to getting the greatest possible range of deviation. As a result, we have chiefly patients with myxedema with subnormal metabolism, and patients with toxic goiters with supernormal metabolism, together with a few patients with essentially normal metabolism.

TABLE 2.—Comparison of Prediction Methods. Data on Obese Persons

| Subject | Age, Years | Height, Cm. | Weight, Kg. | Total Calories per Hour | | | | | Per Cent. Deviation Observed From Predicted | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Observed | Predicted | | | | | | | |
| | | | | | Du Bois Height-Weight Formula | Du Bois Linear Formula | Harris-Benedict | Dreyer | Du Bois Height-Weight Formula | Du Bois Linear Formula | Harris-Benedict | Dreyer |
| Mrs. B. | 44 | 163.0 | 179.0 | 104.4 | 94.3 | 106.2 | 102.6 | 94.5 | +11.5 | —1.7 | +1.7 | +10.5 |
| Mrs. McK. | 48 | 144.5 | 108.0 | 64.7 | 68.4 | 70.6 | 70.1 | 70.8 | —5.3 | —8.4 | —7.7 | —8.7 |
| Mrs. L. L. | 38 | 163.5 | 142.6 | 91.0 | 86.9 | 100.7 | 89.7 | 86.6 | +4.7 | —9.6 | +1.4 | +5.1 |
| Mrs. McI. | 46 | 157.5 | 127.0 | 84.2 | 79.6 | 82.4 | 81.1 | 79.1 | +5.8 | +2.2 | +3.9 | +6.5 |
| Mrs. Sha. | 50 | 155.0 | 110.2 | 75.3 | 74.8 | 79.6 | 77.3 | 78.0 | +0.8 | —5.2 | —2.6 | —3.4 |
| Mrs. F. | 53 | 165.0 | 141.0 | 88.0 | 83.3 | 90.3 | 85.9 | 81.8 | +5.6 | —2.6 | +2.4 | +5.1 |
| Average deviation without regard to sign | | | | | | | | | 5.6 | 4.9 | 3.3 | 6.5 |
| Average deviation with regard to sign | | | | | | | | | +3.8 | —4.2 | —0.1 | +2.5 |

In Figure 1 are compared the deviations by the Du Bois height-weight chart method, with those by Harris-Benedict. A glance at this will show that the two methods give essentially parallel results. The Harris-Benedict deviations are generally a few points higher than the Du Bois ones. A similar comparison has already been made by Boothby and Sandiford,[4] and we were gratified to find that our own results are very nearly identical to theirs. For example, Boothby and Sandiford found the average deviation 6.5 points higher by Harris-Benedict than by Du Bois, while we found it 6.0 points higher. Similarly, 48 per cent. of their observations varied within ± 2.5 points of their average and 87 per cent. within ± 7.5 while 45 per cent. of our observations varied within ± 2.0 points of our average and 88 per cent. were within ± 6 points.

We also studied our cases to see whether those in whom the difference in the two methods was either much greater or much less than the average difference, were all of one sex or of one nutritional extreme. No such relationship was found.

We next determined the average difference between Harris-Benedict and Du Bois deviations in separate groups of patients. We divided the whole series into fourteen groups according to the deviations by the Du Bois method. Each group covered a range of ten points. We then determined the average (Du Bois)—(Harris-Benedict) difference for each group. The results are indicated by the interrupted diagonal line in Figure 1. While the average difference for the whole series, as has been said, was 6.0 points, it will be seen that at the lower end, that is to

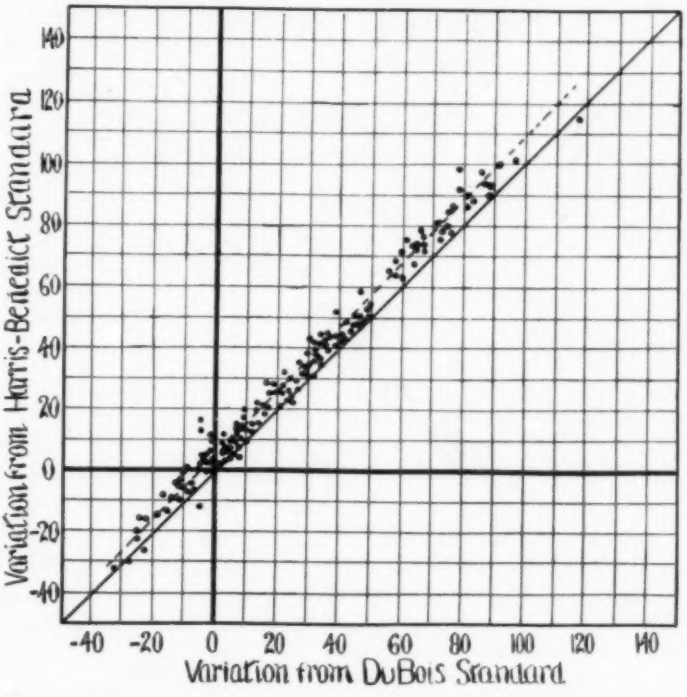


Fig. 1.—Basal metabolism deviations of 160 patients by the Harris-Benedict (ordinates) and Du Bois height-weight formula (abscissae). The per cent. deviation above or below the predicted metabolism is shown on the margin. The interrupted line represents the average of the individual points.

say in the neighborhood of a deviation of — 20 per cent. it is only 4 points, while at the upper end in the neighborhood of a deviation of + 80 per cent. it is 8 points. In this connection it will be remembered that in the Carpenter series of normal men the Harris-Benedict deviation averaged 2.15 points higher than the Du Bois (Table 1).

These relationships we believe are interesting, for they seem to show that there is no fundamental difference in principle between the

Du Bois and the Harris-Benedict methods. Indeed, as Boothby and Sandiford have properly pointed out, the two methods are constructed on identical factors, stature, weight, sex and age. The difference in the two methods is essentially merely a systematic difference in the selected standards. The Sage Institute standards throughout are a little higher than the Harris-Benedict. This, as Du Bois has suggested to us in a recent letter, may have been because most of the subjects used in making the Sage standards were observed in hourly periods in the calorimeter,

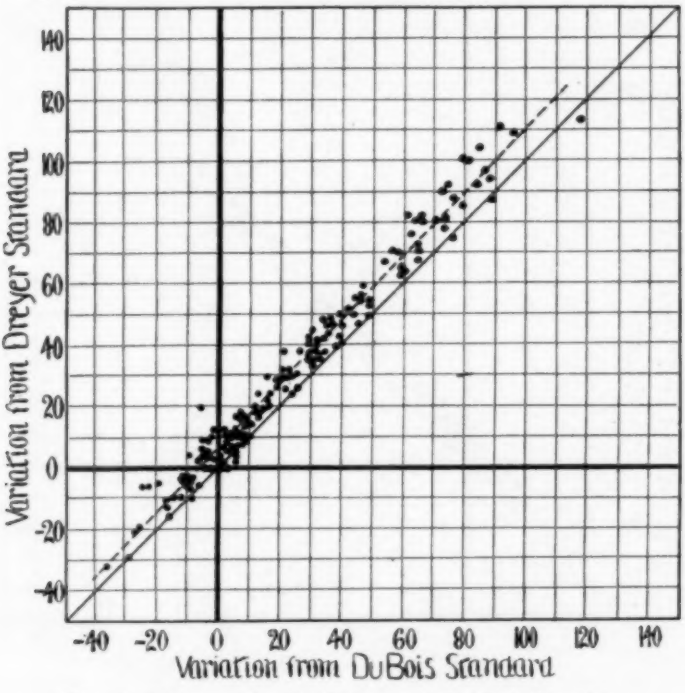


Fig. 2.—The same for the Dreyer and Du Bois formulas.

while a considerable number of Benedict's were observed in short periods with respiration apparatus. As Du Bois further suggests it is not improbable that the subjects were slightly quieter during the shorter periods.

As a matter of fact what all this boils down to is that if approximately 1.8 calories be subtracted from each of the Sage Institute standards, and if they then be employed as before, the results obtained in this series of patients will be essentially like those obtained by the Harris-Benedict method, that is to say, the (Harris-Benedict)—(Du

Bois) difference will be within ± 2 points in about 40 per cent. of the cases, and within ± 6 points in about 85 per cent. more. Furthermore, the difference will be just as likely to be positive as negative.

We next compared the deviation by the Du Bois and Dreyer methods. The results are shown in Figure 2. They are very similar to those of Figure 1. The Dreyer deviations averaged 7.3 points higher than the Du Bois. Thirty-eight per cent. of the Du Bois-Dreyer differences varied within ± 2 points of the average difference and 75 per cent. within ± 6 points.

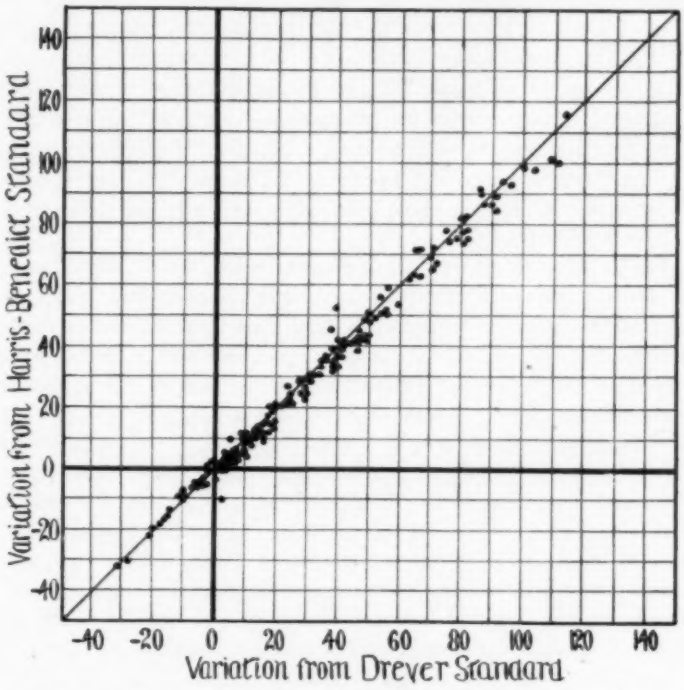


Fig. 3.—The same for the Harris-Benedict and Dreyer formulas.

A comparison of Dreyer deviations with Harris-Benedict deviations is given in Figure 3. It shows a very striking parallelism between the two methods. The Dreyer averaged 1.3 points higher than the Harris-Benedict, and 66 per cent. of the differences were within ± 2 points of the average difference and 88 per cent. within ± 4 points.

## DISCUSSION

We are now in a position to discuss the relative merits of the Du Bois, the Harris-Benedict, and the Dreyer methods, at least in so far

as they concern the clinician who wishes to get an accurate idea of the degree of abnormality of his patients' basal metabolism.

In predicting the metabolism of normal men it was found that the three methods gave about equally good results, that in predicting that of obese subjects the Harris-Benedict method gave slightly better results than the other two. In the matter of deviations from normal in patients with myxedema, toxic goiter and the like, it was found that the information gained by the three methods was again strikingly similar.

The deviations by the Du Bois method are consistently somewhat less than those by the other two, but as has been pointed out this difference can be abolished by a slight change in the Sage Institute standards. These standards are probably too high by somewhere between 1.8 and 0.6 calories. It is only fair to call attention to the fact that Du Bois and his co-workers have said in print that the standards would have to be revised from time to time as more and more normal data accumulated.[16]

We have yet to answer the original question, which method should the clinical calorimetrist use. The answer is obviously that in one sense it is really of small consequence which he uses since the results obtained with the three are so similar. Uniformity, however, is always advantageous and it is best not to abandon an old method for a new one, unless the new presents some material advantage over the old. The Du Bois method is the one in common use today. Since neither the Harris-Benedict nor the Dreyer methods have made any material improvement on it we believe it wise to continue with it, and especially in view of the fact that the existence of calorimetry in the clinic of today is due in large measure to the work of Du Bois. He was the first to devise a satisfactory surface area formula, and also the first to provide standard figures for normal metabolism, both of which were necessary before calorimetry could be added to the diagnostic armamentarium of the clinic or to the list of tests of function.

## SUMMARY AND CONCLUSIONS

1. The accuracy of prediction of the basal metabolism of normal men by the Du Bois height-weight surface area method, the Harris-Benedict multiple prediction tables and by the Dreyer body weight formula, have been compared. It was concluded that the average deviation was essentially the same by each, though the Du Bois deviations tended to run about two points or more lower than either of the others.

2. The same study was made in a series of six obese subjects. It was found that with them the Harris-Benedict method gave a slightly

closer prediction than the other two. In general, however, the deviations by all three methods were within what may be considered a normal limit of variation in all of the six subjects. This furnishes confirmation of the conclusions drawn in earlier papers that there is no fundamental change in basal metabolism in simple obesity.

3. In abnormal subjects patients with hypothyroidism or hyperthyroidism, for example, it was found that the deviations by the three methods were essentially parallel, though on an average the Harris-Benedict deviation tended to be about 6 per cent. higher and the Dreyer about 7 per cent. higher than the Du Bois. It was pointed out that these differences could be practically abolished by a slight reduction in the Sage standards.

4. It is suggested, that although the deviation by the three methods are very similar, nevertheless, it is desirable to have uniformity, and that, therefore, the Du Bois method be continued, since it already is in common use and since the others appear to possess no material advantage over it.

# THE BLOOD UREA NITROGEN IN ACUTE INTESTINAL OBSTRUCTION

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The subject of acute intestinal obstruction has attracted interest for a considerable time both from a clinical and experimental standpoint. Ever since it was found that acute intestinal obstruction was amenable to operative therapeusis, surgeons have urged the early diagnosis of this condition, because they had learned that the success of their operative procedures was largely dependent on relieving the obstruction before the toxemia, which so conspicuously accompanies this condition, overwhelms the patient. The early recognition of acute intestinal obstruction, however, not infrequently presents difficulties even to skilled and experienced observers, chiefly due to the absence of the classical symptoms of the disease which often do not make their appearance until the intoxication has advanced to an alarming degree. In recent years the development of blood chemistry methods and their application, first, in clinical cases, and, later, in experimental cases of intestinal obstruction, have shown a striking elevation in the blood urea nitrogen and noncoagulable nitrogen, and have suggested the possible value of these determinations in diagnosis. The purpose of this communication is to describe a brief series of cases of acute intestinal obstruction and to report the observations which were made on the blood urea nitrogen.

In 1914, Tileston and Comfort,[1] in the course of a study of the blood chemistry in a large series of miscellaneous cases in human beings, found that in three cases of acute intestinal obstruction there was a surprisingly high elevation of the blood urea nitrogen and noncoagulable nitrogen. In these cases the blood urea nitrogen varied from 59 to 77 per cent. of the total noncoagulable nitrogen. Their highest blood urea nitrogen in a case of obstruction terminating in recovery was 92 mg. per 100 c.c. and their lowest reading was 45.5 mg. In a case of acute obstruction due to an intestinal band which terminated fatally in spite of operation, the blood urea nitrogen rose from 72.8 mg. at the time of operation to 114 mg. immediately prior to death. The phenolsulphonephthalein excretion was determined in two cases. In the first case it varied from 25 to 43 per cent., whereas in the second case it was 70 per cent. in 2 hours and 10 minutes.

1. Tileston, W., and Comfort, C. W.: Arch. Int. Med. **14**:620 (Nov.) 1914.

The study of the blood chemistry in acute intestinal obstruction was then taken up by Cooke, Rodenpaugh and Whipple,[2] who investigated the subject from an experimental basis. They produced acute intestinal obstruction and closed intestinal loops in dogs, and found that in the vast majority of cases there was a definite increase in the noncoagulable nitrogen which was apt to be more striking and constant in the cases associated with symptoms of acute intoxication. They were of the opinion that the determination of the noncoagulable nitrogen was of more value than the blood urea nitrogen, as the former was more uniformly elevated in cases of acute intestinal obstruction, whereas the latter in their series of cases varied from 30 to 60 per cent. of the total noncoagulable nitrogen. They believed that the determination of the noncoagulable nitrogen might be of value in the diagnosis and prognosis of human cases.

Whipple and his co-workers, in addition to many contributions on the nature of the substance responsible for the toxemia which is such an impressive feature of the clinical picture of acute intestinal obstruction, have studied the renal function in cases of experimental obstruction and proteose intoxication. McQuarrie and Whipple [3] found that associated with the intoxication of acute intestinal obstruction there exists a definite impairment of the excretory function of the kidney, as shown by a decrease in the ratio of urea and sodium chlorid excretion and a decrease in the percentage output of phenolsulphonephthalein. It is interesting to note that the alteration in the urea and sodium chlorid excretion is far more pronounced than the decrease in the excretion of phenolsulphonephthalein, and that a marked decrease in the output of the dyestuff occurred mainly immediately before death.

McQuarrie and Whipple [4] then studied the renal function as influenced by proteose intoxication, and found that when toxic proteose material obtained from a closed intestinal loop was injected intravenously, there followed a definite lowering of the excretory function of the kidney similar to that observed in experimental intestinal obstruction. Injection of other proteose substances obtained from various sources did not have this effect on renal function. This work of McQuarrie and Whipple is of particular interest in connection with studies by Longcope and Rackemann [5] of renal function in cases of hypersensitive individuals. They found that in three of six cases of urticaria, four of which were hypersensitive to one or more foreign

2. Cooke, J. V.; Rodenpaugh, F. H., and Whipple, G. H.: J. Exper. M. **23**:717, 1916.

3. McQuarrie, I., and Whipple, G. H.: J. Exper. M. **29**:397, 1919.

4. McQuarrie, I., and Whipple, G. H.: J. Exper. M. **29**:421, 1919.

5. Longcope, W. T., and Rackemann, F. H.: J. Urol. **1**:351, 1917.

proteins, there was a definite disturbance in the functional activity of the kidney. One of the cases reported by Longcope and Rackemann was admitted to the hospital with the diagnosis of uremia and the finding of a blood urea nitrogen of 150 mg. per 100 c.c. at first seemed to confirm this diagnosis. The subsequent clinical course, however, showed that the case was one of sensitization to foreign protein and that the urea retention was probably due to proteose intoxication and its effect upon protein catabolism and renal function.

The group of cases which are herewith reported are seven in number and with two exceptions are cases of acute intestinal obstruction occurring after operation for some surgical disease of the abdomen. The first of the ante-operative cases was a woman aged 56 years who was ill for seven days with vomiting and marked abdominal distention and in whom operation revealed an annular carcinoma of the sigmoid. The second of the ante-operative cases was a woman 57 years old who was being treated in the hospital for a severe form of diabetes. While under observation, she developed marked obstipation and abdominal distention, and operation showed marked distention of small intestine with fecal impaction in the colon. All of the postoperative cases of intestinal obstruction, with one exception, terminated fatally, and postmortem examination was obtained in all but one of the fatal cases. In the case in which necropsy was not permitted, the patient succumbed three weeks later to the continuous loss of fluid and presumably nutriment through the enterostomy wound. The blood chemistry determination which was done in all cases was the blood urea nitrogen by Van Slyke and Cullen's modification of Marshall's method. The noncoagulable nitrogen was not done. In one case the phenolsulphonephthalein excretion was studied.

## REPORT OF CASES

Case 1.—E. B., female, aged 32 years, was admitted to the Presbyterian Hospital March 22, 1919, with the complaint of severe pain in the epigastrium, radiating around the right costal margin into the back. Pain was of two days' duration and was accompanied by repeated vomiting. The stools were light colored, and the urine was dark amber. She had had several similar attacks during the past ten years.

Physical examination showed jaundiced sclerae and tenderness in the right upper quadrant.

Patient was operated on March 24, 1919, and a chronically inflamed and contracted gallbladder, bound down by adhesions to the liver and pylorus, was found. There were several gallstones in the gallbladder, one in the common duct and three at the papilla of Vater. The common duct was opened, the stones were removed and the duct closed. The gallbladder was removed in the usual fashion and a rubber drain placed in Morrison's pouch.

March 24. Patient has made a fairly good immediate recovery from operation. She has vomited small amounts of bile tinged fluid but is otherwise comfortable.

March 25. Patient does not look well. Pulse is 110 and easily compressible. There is a moderate degree of distention. She looks toxic.

March 26. Patient is very much worse. Her eyes are sunken, facies is drawn, and she looks profoundly toxic. Abdomen is not markedly distended and is only slightly tender. She has vomited about 30 c.c. of dark-brown fluid, but passage of stomach tube returned a large amount of almost black fluid with odor of upper intestinal material. Pulse is 140 and is very soft in quality. Colon irrigation returns clear with slight flatus.

March 30. Patient is irrational, and pulse is small and rapid. She is vomiting repeatedly. Abdominal distention and tenderness are very slight. She has no pain in her abdomen.

April 3. Blood urea nitrogen, 147 mg. per 100 c.c.; hemoglobin, 80 per cent.; red blood cells, 5,200,000; white blood cells, 30,000; polymorphonuclears, 87 per cent.; lymphocytes, 13 per cent.

April 4: The patient was seen in consultation by the medical service who found no evidence of chronic renal trouble or chronic disease as a basis for the patient's condition. It was felt that the high blood urea nitrogen was due to acute renal insufficiency which was thought to be due to some underlying disturbance of undetermined nature.

April 5. Condition of patient is distinctly improved. Color is better and eyes are brighter. Blood urea nitrogen, 132 mg. per 100 c.c.

April 7. Patient feels a great deal better but complains of intense itching from hives. Examination shows a marked generalized eruption of urticarial character.

April 8. Blood urea nitrogen, 50 mg. per 100 c.c.

April 10. Eruption has disappeared entirely. Patient is well on the road to recovery, and is eating with considerable appetite.

April 23. Patient was discharged feeling fine.

April 22, 1920. Patient was seen in the follow-up clinic and found to be in excellent health.

The clinical picture which this patient presented was very confusing, and, except for the frequent vomiting, was not typical of intestinal obstruction. The blood urea nitrogen was, therefore, of great interest as pointing to this condition as the cause of the patient's toxemia, and although the exact nature of the obstruction was not determined, there is little conjecture as to its existence. An unusual feature of the case was the appearance of an urticarial eruption during the convalescence of the patient. In the light of Whipple's work on the nature of the substance responsible for the toxemia of intestinal obstruction and the well recognized rôle of foreign proteins in the production of cutaneous lesions, it seems fair to assume that the urticarial eruption was simply a manifestation of proteose intoxication subsequent to the intestinal obstruction.

CASE 2.—H. P., male, aged 21 years, was admitted to the Presbyterian Hospital, Jan. 17, 1920, with the complaint of pain in the abdomen of thirty-six hours duration. The pain was first situated in the epigastrium where it was dull in character, but two hours later it localized in the right lower quadrant where it became sharp and cramplike. He vomited several times after the onset of the pain.

Physical examination showed definite right rectus rigidity with a marked degree of localized tenderness over McBurney's point. White blood cells, 17,500; polymorphonuclears, 90 per cent.; lymphocytes, 10 per cent. Urine: amber, clear, acid, specific gravity, 1.024; albumin, 0; glucose, 0; microscopic, negative. Operation Jan. 17, 1920, showed an acutely inflamed appendix with a perforation in its middle third and considerable free fluid in the pelvis. Appendix was removed in the usual fashion and rubber-tube drains inserted into the pelvis.

January 18. Patient has made a good recovery from operation without nausea or vomiting. There is no distention.

January 19. There is no distention and patient is very comfortable.

January 21. Patient has been considerably distended for the past thirty-six hours and is complaining of severe cramplike abdominal pain. There has been no relief from rectal treatments. Pulse has increased from 100 to 120 and the patient looks badly. He has vomited large amounts of brownish material several times.

January 22. All of the patient's symptoms have increased in severity. Blood urea nitrogen, 54 mg. per 100 c.c.

January 23. Patient was operated on and the small intestine was found to be greatly distended and congested, whereas the large intestine was completely collapsed. No acute change from distended to collapsed intestine was found, there being a gradual transition from nondistended ileum at the ileocolic junction to a point about 3 feet proximal to the cecum where the ileum was distended to twice its normal diameter. It was felt that in separating the coils of intestine from the drainage tubes, a mechanical obstruction had been relieved before its exact nature could be studied. Enterostomy tube was inserted into the ileum about 2 feet above the ileocecal junction.

The patient had a very stormy postoperative course which finally terminated fatally twenty days after his second operation. He developed a severe pneumonitis from which he recovered only to lapse into a stage of marked inanition due to continuous loss of fluid and nutriment through his enterostomy wound. All attempts to divert the stream of intestinal contents into the distal loop of enterostomy were futile.

This case presented a straightforward picture of acute intestinal obstruction with all the cardinal symptoms. The finding of a blood urea nitrogen of 54 mg. in the absence of any signs of pre-existing renal disease confirmed the clinical diagnosis.

Case 3.—W. H., male, aged 49 years, was admitted to the Presbyterian Hospital, Feb. 10, 1920, with the complaint of pain in the lower abdomen of twenty-four hours' duration. One week previously he had been ill for three days with a streptococcus sore throat from which he had apparently recovered. He became nauseated and vomited several times shortly after the onset of the pain.

Physical examination showed moderate degree of abdominal distention with tenderness in both lower quadrants. White blood cells, 14,400; polymorphonuclears, 89 per cent.; lymphocytes, 11 per cent. Urine: amber, clear, acid; specific gravity, 1.034; albumin, 0; glucose, 0; microscopic, negative.

Operation Feb. 10, 1920, showed an acutely inflamed appendix extending across the abdomen to the left wall of the pelvis, where it was adherent, binding down and obstructing the sigmoid. Small intestine and large intestine above the level of the obstruction were greatly distended. The appendix was removed in the usual fashion and rubber tube drains inserted in the pelvis.

February 11. The patient made a fairly good recovery from operation but is still distended. Colon irrigations returned a moderate amount of gas and fecal matter.

February 16. Distention is very marked, in spite of all treatment. Patient has grown weaker, and pulse has grown more rapid and is of poorer quality. A secondary operation was performed this morning, and an enterostomy tube inserted into the presenting loop of dilated small intestine. On account of patient's condition, exploration was not performed, but small intestine appeared greatly distended.

February 18. Enterostomy tube is draining freely, but patient's condition has grown worse. He is apathetic, weak and has occasional twitching of the arms. Blood pressure: systolic, 92; diastolic, 68. Urinary output for the past twenty-four hours has been only 50 c.c. in spite of an intake of 2,500 c.c. of fluid given intravenously and by hypodermoclysis. Blood urea nitrogen, 106 mg. per 100 c.c.

February 19. Patient is comatose. Breathing is stertorous. Pulse is slow and quite full. There has been complete anuria for the past twenty-four hours. Blood urea nitrogen, 170 mg. per 100 c.c. Patient died that afternoon.

Necropsy showed marked distention of the stomach and jejunum above the level of the jejunostomy. Below this the intestine was collapsed. No definite organic obstruction was demonstrated. The kidneys together weighed 270 gm. They were normal in size and slightly softer than usual. The capsule was glistening and stripped easily. External surface of kidneys showed evidence of lobulation and was irregularly congested. On cut section the striations were easily made out, but between the striations there seemed to be swelling of cortical tissue. Glomeruli were easily visible as shiny points. Medulla and pyramids were normal. Microscopic examination showed a few areas where the glomeruli were fibrosed with collapse of adjacent tubules. Throughout the remainder of the sections the glomeruli were congested and completely filled their capsules, but there were no adhesions between glomerulus and capsule. The convoluted tubules were slightly swollen so that their lumens were small, but cell outlines and nuclei were well preserved.

This case, although undoubtedly one of acute intestinal obstruction, is puzzling in so far as the cause of the obstruction was not determined. It was at first believed that it was one of paralytic ileus, and the absence of cramps and visible peristalsis supported this belief. However, the fact that all colon irrigations returned without gas or fecal material pointed to the presence of a complete obstruction of organic nature, and this impression was confirmed by the postmortem findings of distention of the upper jejunum and collapse of the remainder of the intestine. A striking feature of the clinical picture was the marked decrease in the excretory function of the kidney, as shown by the almost complete anuria which lasted for a period of forty-eight hours prior to death. Associated with this renal insufficiency he developed involuntary twitchings of the arms not unlike those seen in uremic states, and later lapsed into a condition of coma. These symptoms were not the result of any inflammatory process in the kidney, as pathological examination failed to show any of the morphological changes which usually accompany nephritis, but were due to the lowering of renal function which follows intestinal obstruction and proteose intoxication.

CASE 4.—M. J., female, aged 60 years, entered the Presbyterian Hospital, March 6, 1920, with the complaint of passage of bright red blood from the rectum of three months' duration.

Physical examination was essentially negative, except for the presence of a hard mass situated on the anterior rectal wall, which pathologic examination showed to be a typical adenocarcinoma. March 11, 1920, the rectum and the lower portion of the sigmoid were removed by the combined abdominoperineal method. During the latter part of the operation, the patient went into a state of shock presumably on account of traction on the mesentery. She remained in this state for approximately thirty-six hours, and then gradually lapsed into an apathetic stage interrupted by occasional periods of restlessness. She refused food constantly and fluids were administered by infusion and hypodermoclysis. Feedings through stomach tube were futile, as they were vomited shortly afterward. Distention was moderate, but there were no cramps or visible peristalsis. Blood urea nitrogen, March 17, was 99 mg. per 100 c.c. Blood pressure: systolic, 115; diastolic, 70. Urine showed a faint trace of albumin but was otherwise negative. Specific gravity varied from 1.018 to 1.012. Patient grew steadily worse and died April 4, 1920.

Necropsy showed a loop of small intestine adherent to parietal peritoneum at upper part of operative incision. Above this level the small intestine was moderately distended with fluid and gas. Below the level of the obstruction the intestine was collapsed. The kidneys together weighed 300 gm. They were flabby and of equal size. Left kidney showed that the capsule stripped easily exposing a slightly rough, pale pink surface. About the middle of the organ there was a mottled reddish-yellow scar which on section appeared to be an old infarct. The cortex measured 4 mm. in width and was pale with inconspicuous glomeruli. The striations were indefinite but many straight congested vessels were seen in the cortex. Medulla was grossly normal. Pelvis was considerably dilated and congested in streaks. The right kidney presented the same appearance except for the absence of any infarct Microscopic examination showed the glomeruli and tubules to be normal There were no changes in the blood vessels Section through the old infarct in the left kidney showed an area of coagulation necrosis extending from cortex into peripheral portion of medulla. Shadows of glomeruli and tubules were still present.

Case 5.—A. R., female, aged 62 years, entered the Presbyterian Hospital, April 4, 1920, with the complaint of pain in the abdomen, cramps and vomiting of twenty-four hours' duration. For the past fourteen years she had had an umbilical hernia which had always been easily reducible until forty-eight hours ago when she found that she could not replace the mass within the abdomen.

Physical examination showed a profoundly toxic, elderly woman with a greatly distended abdomen. At the umbilicus there was a large, tender irreducible hernia.

Operation was performed April 4, 1920. The contents of the hernial sac was the entire transverse colon, which was so greatly distended with gas that it had to be punctured twice before it could be returned to the abdominal cavity. The patient made a good recovery from operation and was in excellent condition for three days. On the fourth day she began to look poorly, and the abdomen was considerably distended. She appeared to be listless and apathetic, and these symptoms grew steadily worse. April 10, 1920, blood urea nitrogen, 140 mg. per 100 c.c. April 12, 1920 the patient was given a hypodermoclysis of 1,000 c.c. of physiologic sodium chlorid solution and at the end of the treatment 6 mg. of phenolsulphonephthalein was given intramuscularly, after the patient had been previously catheterized. At the end of two hours and ten minutes, patient was again catheterized and 230 c.c. of urine obtained. Phthalein excretion was 58 per cent. Blood urea nitrogen on the same day was 130 mg. Blood pressure was not elevated. April 9, 1920: systolic, 135; diastolic, 70. April 11, 1920: systolic, 130; diastolic, 65. Urine examination was completely negative. There was no albumin and no casts. Specific gravity varied from 1.014 to 1.026. The patient's condition grew progressively worse and she died on April 14, 1920.

Necropsy showed the colon to be collapsed from the hepatic flexure to the rectum. At the hepatic flexure there were a few relatively firm adhesions, and this was found to be the site where the intestine had been punctured during operation. Above this point the colon and small intestine were tremendously distended. The kidneys together weighed 280 gm. They were of equal size and similar in appearance. The capsule stripped easily exposing a gray surface with distended stellate veins. On section, the cortex was normal in width with distinct striations. The glomeruli were normally prominent. In the lower pole of the right kidney there was a small, yellow rectangular infarct. Microscopic examination showed the tissue to be poorly preserved, probably through postmortem changes. The glomeruli were normal, except for occasional slight thickening of the capsule. The tubules presented no abnormality. There were no changes in blood vessels. Section through infarct showed an area of coagulation necrosis extensively infiltrated with red blood cells.

ANALYSIS OF URINE AND BLOOD

| Case | Name | Age | Date | Urine | | | Blood Urea N, Mg. per 100 C.c. | Blood Pressure | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Specific Gravity | Albumin | Casts | | | |
| 1 | E. B. | 32 | 4/ 3/19 | 1.030 | + | 0 | 147 | ..... | Acute ileus following cholecystectomy and common duct drainage; obstruction relieved spontaneously |
| | | | 4/ 5/19 | 1.021 | ++ | 0 | 132 | | |
| | | | 4/ 8/19 | 1.022 | ++ | 0 | 50 | | |
| 2 | H. P. | 21 | 1/22/20 | 1.024 | 0 | 0 | 54 | ..... | Acute ileus following appendicectomy with drainage; obstruction in region of ileocecal junction |
| 3 | W. H. | 49 | 2/18/20 | 1.034 | 0 | 0 | 106 | 92/68 | Acute ileus following appendicectomy with drainage; obstruction in lower jejunum |
| | | | 2/19/20 | Q.N.S. | + | 0 | 170 | 94/60 | |
| 4 | M. J. | 60 | 3/17/20 | 1.018 | + | 0 | 99 | 115/70 | Acute ileus following resection of carcinoma of rectum; upper intestinal obstruction due to adhesions |
| 5 | A. R. | 62 | 4/10/20 | 1.026 | 0 | 0 | 140 | 135/70 | Acute ileus following repair of strangulated umbilical hernia; obstruction at hepatic flexure of colon |
| | | | 4/12/20 | 1.014 | 0 | 0 | 130 | 130/65 | |
| 6 | A. B. | 56 | 4/21/20 | 1.018 | + | + | 74 | 98/75 | Acute ileus due to a constricting annular carcinoma of sigmoid |
| 7 | A. M. | 57 | 10/26/20 | 1.012 | 0 | 0 | 60 | 145/10( | Acute ileus due to fecal impaction in colon |

In this case the question arose as to whether or not the high blood urea nitrogen might be caused by a chronic nephritis. Against this diagnosis was the absence of high blood pressure, the negative urinary findings, with a variation in specific gravity from 1.014 to 1.026 and a phenolsulphonephthalein excretion of 58 per cent. It was felt that if the elevation of the blood urea nitrogen were due to a chronic nephritis, the phthalein excretion would be greatly lowered, whereas in acute intestinal obstruction as shown by McQuarrie and Whipple, the phthalein excretion is not greatly altered until shortly before death.

CASE 6.—A. B., female, aged 56 years, entered the Presbyterian Hospital with the complaint of distention of the abdomen of one week's duration.

Physical examination showed a profoundly ill, elderly woman with an enormously distended abdomen. There was no visible peristalsis. Blood pressure was 98 systolic and 75 diastolic. White blood cells, 11,600; polymorphonuclears, 77 per cent.; lymphocytes, 23 per cent. Urine showed a very faint trace of albumin with a rare finely granular cast. Blood urea nitrogen was 74 mg. per 100 c.c. Operation was performed April 21, 1920, and showed an annular

carcinoma of the sigmoid with tremendous distention of the intestine above this level. There was a small perforation in the transverse colon. This was closed and a large enterostomy tube inserted in the descending colon. Although the patient stood the operation well, she lapsed into a state of marked apathy and died six hours later. No necropsy was obtained, but it was felt that in the absence of any signs pointing to chronic nephritis, the high blood urea nitrogen was due to the toxemia of intestinal obstruction. This case, as did the preceding one, demonstrated that an elevation of the blood urea nitrogen can occur following a low obstruction as well as a high intestinal obstruction.

Case 7.—A. M., female, aged 57 years, entered the Presbyterian Hospital, July 7, 1920, with the complaint of weakness, loss of weight, polydipsia and polyuria of five months' duration. Urine examination showed glucose 2.6 per cent. and the blood sugar was 0.43 per cent. She was fasted for several days and placed on a restricted diet under the influence of which she gradually became sugar free. Oct. 22, 1920, she complained of severe abdominal cramps and obstipation. She was given catharsis without effect and enemas were returned clear. After four days of marked abdominal distention, cramps and failure to pass either gas or feces, the patient was operated on, and the large intestine found filled with impacted fecal material while the small intestine was greatly distended with gas. Blood urea nitrogen taken the day before operation was 60 mg. per 100 c.c. The patient was in very poor shape at time of operation, and died shortly afterward. Blood urea nitrogen previous to onset of obstipation was not done, as the patient was apparently an uncomplicated diabetic, but it was felt, nevertheless, that the blood urea nitrogen of 60 mg. presented an abnormal elevation resulting from her ileus.

## SUMMARY

Seven cases of acute intestinal obstruction are described, in all of which there was an increase in blood urea nitrogen. The lowest reading was 54 mg. per 100 c.c. The highest reading was 170 mg.

In one case in which the blood urea nitrogen was 130 mg. per 100 c.c., the phenolsulphonephthalein excretion was studied and found to be 58 per cent. in two hours and ten minutes.

In one case a generalized urticarial eruption appeared while the patient was convalescing from an acute ileus. As the substance which causes the toxemia of acute intestinal obstruction is presumably of proteose nature, it was felt that this eruption was probably a cutaneous manifestation of proteose intoxication.

All cases were free from any evidence of chronic renal disease, and it is, therefore, fair to assume that the elevation in the blood urea nitrogen was the result of the acute intestinal obstruction.[6]

I wish to express my indebtedness to Dr. A. V. S. Lambert, Director of the Surgical Service, for the privilege of reporting these cases, to Dr. W. T. Longcope, Director of the Medical Service, for many helpful suggestions and to Dr. J. W. Jobling, Director of the Pathological Service for the use of the pathological material.

6. After this communication was in proof, an article by I. M. Rabinowitch was published in the Canadian Medical Association Journal for March, 1921, in which an increase in the blood urea nitrogen was reported in a series of cases of intestinal obstruction, acute general peritonitis and acute pancreatitis.

# BOOK REVIEWS

LAENNEC APRES 1806; 1806-1826; D'APRES DES DOCUMENTS INEDITS. Alfred Rouxeau (Professeur à l'Ecole de médecine de Nantes). 80, Paris, 1920. J. B. Baillière et Fils, 19 Rue Hautefeuille, Fr. 35.

The publication in 1912 of the first volume of Professor Rouxeau's life of Laennec (Laennec avant 1806, etc. 80 Paris, 1912, J. B. Baillière et fils) was a happy event for those who cherish the memory of one of the great figures in the history of medicine. And now, after more than eight years, comes the conclusion. Filled with a just admiration of the man and his work, together with the pride of a compatriot in the accomplishments and contributions of a fellow Breton, generously aided by the living members of the Laennec family, Professor Rouxeau has gathered a remarkably full material bearing on the life and career of the discoverer of auscultation.

From a minute and judicial study of this material, and from a personal familiarity with the scenes which surrounded Laennec's boyhood, the author has constructed faithfully, lovingly, sympathetically, the narrative of his career. One follows step by step from boyhood onward the development of a great character. The wealth of quotation from personal letters gives one a rare insight into the spirit of the man, and lends a peculiar personal charm to the picture.

To Professor Rouxeau we owe a debt of sincere gratitude for weaving together so skilfully the threads of a story which should be familiar to every physician who loves the history of his art.

W. S. T.

WIENER ARCHIV FUER INNERE MEDIZIN. Herausgegeben von Priv.-Doz. Dr. Richard Bauer, Prof. Dr. Rudolf Jaksch, etc. Geleitet von W. Falta und K. F. Wenckebach, Urban und Schwarzenberg, Berlin und Wien.

When the history of the work of physicians and biologists during the world war comes to be written, it will probably appear that one of the finest figures will be that of the modest, well trained and unselfish K. F. Wenckebach, who, called to the University of Vienna when it was an honor to be there, chose to remain when the sword of Brennus had made life almost impossible. What he and others have done to keep up the courage of the rest of the population we can dimly surmise. This new Archiv is a promising example of the spirit of the medical Viennese. The old format is retained, the old standpoint, clinical and experimental, if the experiment bears on a clinical problem. Fascicles of from ten to fifteen quires are expected at irregular periods, forming volumes of from thirty to forty quires. No price is given. How can it be in a country where paper money is of less value than beer bottle labels? No longer the good paper of old. Yet the type and presswork are good, the proofreading better than much of ours. The illustrations are few and only black and white.

The table of contents of Volume 2, Part 1, shows interesting material. Egmont Muenzer of Prague returns to the study of vascular sclerosis, in which he contrasts sclerosis of the larger and smaller (precapillary) arteries, and as a cause of arteriolo-capillary sclerosis he suggests acute infectious disease and gout.

Edmund Maliwa and Miss Eckert of Innsbruck have an article concerning chlorin metabolism in histogene edemas, with a criticism of Ambard's law on the relation between chlorid concentration in serum and excretion in urine. They think the law is not valid in edemas, but applies after their removal.

Arnold Kirch of Vienna writes on concretio and accretio cordis. He takes a case wrongly diagnosed by Baeumler to show how easy it is to make a mistake, so that concretion may be diagnosed and the necropsy show no signs; on the other hand, the necropsy gives the first intimation. He speaks of the signs advanced by various authorities, such as absence of systolic apex beat, rebound of the thorax, diastolic filling of cervical veins, Broadbent's sign, immobility of apex beat and dulness on change of position, paradox pulse, metallic heart sounds, constant doubling of the second sound at the apex and the work of Wenckebach with relation to the movement of the thorax. The author advances a new pulse sign—a small pulse easily compressed by the finger, and with low pressure and low pulse pressure (from 10 to 15 mm.). He thinks the condition is usually the sequel of a polyserositis, especially tuberculosis.

Alfred Decastello writes on bacteriemia in typhoid and its treatment by vaccines. He asserts that under vaccine treatment the bacilli disappear from the circulation before the fever, and that at the same time rapid removal of typhoid bacilli takes place from the internal organs. In some cases no such results occur. Success depends on the antibacterial effect, the factors for which cannot yet be stated.

F. Hoegler reports from Falta's clinic a case of chronic polyneuromyositis with severe contractures, giving the differential diagnosis from trichinosis, polymyositis, polyneuritis and muscular atrophy.

Oskar Wellmann in Chvostek's clinic describes the iodin binding power of urine and thinks it gives a useful measure for the analysis of kidney function equal in value to specific gravity. The same author writes on the pathology of edema disease, showing that the pancreas serves as a point of predilection for alimentary poisons.

S. Bondy and R. Strisower, working under Pal, speak of the effect of hypertonic salt solution on hemoglobinuria from cold.

Egon Weiser contributes an article from the German medical clinic of Prague, showing that political frontiers cannot prevent cultural associations, on insufficient expansibility of the heart as a cause of severe circulatory disturbance, with an interesting study of the probable mechanism.

Needless to say, the *Wiener Archiv* must be included among current journals in all medical libraries and its contents examined regardless of the fates of archdukes and kaisers or the rise and fall of kronen.

## CORRECTION

In the paper by C. M. Richter, published in the March issue of the ARCHIVES OF INTERNAL MEDICINE, the legend for Figure 3 was omitted. It reads: Continuous line represents air pressure figures taken at 8 a. m. (Washington, D. C., time) every day; reduced to sea level and standard gravity. Weekly lines give number of deaths from influenza and pneumonia.